

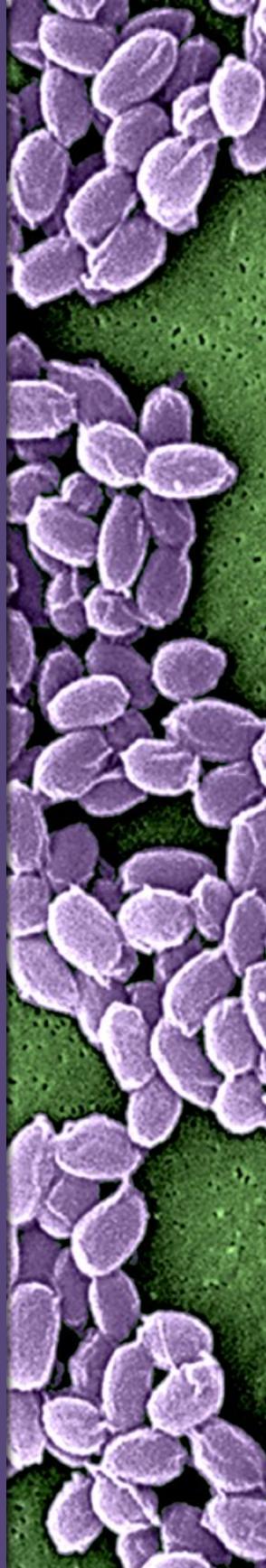


SAFEGUARDING CHILDREN

Pediatric Medical
Countermeasure Research

Presidential Commission
for the Study of Bioethical Issues

March 2013



On the cover: Under a high magnification of 12,483X, this scanning electron micrograph (SEM) depicted spores from the Sterne strain of *Bacillus anthracis* bacteria.

Adapted from: CDC/Laura Rose, 2002



SAFEGUARDING CHILDREN

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Washington, D.C.
March 2013

<http://www.bioethics.gov>

ABOUT THE PRESIDENTIAL COMMISSION FOR
THE STUDY OF BIOETHICAL ISSUES

The Presidential Commission for the Study of Bioethical Issues (the Bioethics Commission) is an advisory panel of the nation's leaders in medicine, science, ethics, religion, law, and engineering. The Bioethics Commission advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Bioethics Commission seeks to identify and promote policies and practices that ensure scientific research, health care delivery, and technological innovation are conducted in a socially and ethically responsible manner.

For more information about the Bioethics Commission, please see <http://www.bioethics.gov>.

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PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES

President Barack Obama
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Secretary Kathleen Sebelius
U.S. Department of Health and Human Services
200 Independence Avenue, SW
Washington, DC 20201

Dear Mr. President and Madame Secretary:

On behalf of the Presidential Commission for the Study of Bioethical Issues, we present to you *Safeguarding Children: Pediatric Medical Countermeasure Research*. In response to the January 6, 2012 request by Health and Human Services Secretary Kathleen Sebelius, the Bioethics Commission conducted a thorough review of the ethical considerations of conducting clinical trials of medical countermeasures (MCMs) with children, including the ethical considerations involved in conducting a pre- and post-event study of anthrax vaccine adsorbed (AVA) for post-exposure prophylaxis with children.

The Bioethics Commission held four public meetings on this topic and heard from many speakers addressing a wide range of issues related to this report. At Secretary Sebelius's request, the Bioethics Commission sought the advice of bioethics and public health ethics scholars, members of stakeholder communities, pediatric research scientists, and officers of local government and federal regulatory agencies. In addition, the Bioethics Commission solicited public comment and received many informative responses.

Safeguarding children is one of our nation's foremost obligations, and the ethical conduct of pediatric MCM research is one of the ways in which our society fulfills its duty to protect children both as individual research participants and as members of society to the greatest extent ethically and practically possible in the event of an attack. Because children substantially lack the developed capacities necessary for adequately informed and voluntary decision making, they cannot consent to participate in research in the relevant ethical and legal sense. Extra protections are therefore necessary to ensure that children are not placed at excessive risk for the benefit of others. The Bioethics Commission offered six recommendations to guide the ethical conduct of pediatric MCM research.

The Bioethics Commission concluded that in the case of pre-event pediatric MCM research, absent exceptional circumstances, all research must be designed to pose only minimal risk to child participants. When pre-event pediatric MCM research cannot be conducted as a minimal risk study, only research that poses no more than a minor increase over minimal risk—a level that is still very limited and poses no substantial risk to health or well-being—should proceed to national-level ethical review under current regulations (45 C.F.R. § 46.407/21 C.F.R. § 50.54). The Bioethics Commission proposed an ethical framework to ensure the thoroughness and ethical rigor of such national-level review. Regardless of whether pre-event research is conducted, post-event pediatric MCM research should be planned in advance and conducted when MCMs are administered to children in an emergency. When untested MCMs are made available to children in an emergency, research protections should be in place.

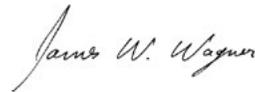
In addition to generally reviewing the ethical considerations of MCM research, Secretary Sebelius requested that the Bioethics Commission specifically address the ethical considerations of pediatric testing of AVA. (The Bioethics Commission has not been provided a protocol to review, nor is it within the purview of the Bioethics Commission to sit as an institutional review board or a national-level review panel under 45 C.F.R. § 46.407/21 C.F.R. § 50.54.) The Bioethics Commission concluded that before ethical pre-event pediatric AVA trials can be considered, further steps must be taken, including additional minimal risk research with adult participants, in order to determine whether the research risks to children—who do not stand to benefit directly from it—can be reduced to a level that poses no substantial risk to their health or well-being.

The Bioethics Commission is honored by the trust you have placed in us and we are grateful for the opportunity to serve you and the nation in this way.

Sincerely,



Amy Gutmann, Ph.D.
Chair



James W. Wagner, Ph.D.
Vice Chair



THE SECRETARY OF HEALTH AND HUMAN SERVICES

WASHINGTON, D.C. 20201

January 6, 2012

Amy Gutmann, Ph.D.
Commission Chair
Presidential Commission for the
Study of Bioethical Issues
U.S. Department of Health and Human Services
1425 New York Ave, NW
Suite C100
Washington, DC 20005

Dear Dr. Gutmann,

The U.S. Department of Health and Human Services is responsible for developing and stockpiling safe and effective medical countermeasures to protect the nation from bioterror attacks. While it has made significant progress toward this goal for adults, the development of appropriate medical countermeasures for children lags, in part due to challenges in collecting basic dose and immunogenicity studies in pediatric populations.

On October 28, 2011, the HHS's National Biodefense Science Board (NBSB) released its report and recommendation on the "Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP)." The NBSB debated how best to obtain scientifically valid safety and immunogenicity data about AVA PEP for children, a complex issue with ethical, scientific, medical, legal, regulatory, and administrative challenges. In its recommendation, the NBSB concludes that it would be in the best interests of children to gather safety and immunogenicity data about AVA PEP in children prior to an anthrax event, rather than during a future crisis when the vaccine may be needed. The NBSB also recommends that such data be obtained only after the ethical considerations are adequately addressed and reviewed by an appropriate body.

To address this issue and the broader question of how best to obtain clinical data on medical countermeasures in children, I ask you, as the Chair of the Presidential Commission for the Study of Bioethical Issues, to convene a panel to conduct a thorough review of the ethical considerations of conducting clinical trials of medical countermeasures in children. I also ask that the Commission include the ethical considerations in conducting a pre- and post-event study of AVA PEP in children as part of its review.

Given the complexity and sensitivity of this issue, I ask that the Commission consult with a range of experts within and outside the United States Government, to include the medical and scientific communities in addition to non-profit organizations and other public constituencies. I ask that the Commission provide me with a report of its findings, as well as any recommendations and suggestions the Commission deems appropriate.

Amy Gutmann, Ph.D.
January 6, 2012
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I would welcome the opportunity to further discuss a timeframe for this project that is mutually agreeable, taking into consideration both the urgency and complexity of the issue. The safety of our children is paramount, and it is vital that we thoroughly address any and all ethical considerations relative to having adequate and available safety and immunogenicity data on our medical countermeasures to protect them before, during, or after an event.

I look forward to reviewing the Commissions's recommendations on this critical component of improving and advancing our nation's resilience, preparedness, and response efforts.

Sincerely,



Kathleen Sebelius

Thank you for your continued leadership

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ACKNOWLEDGEMENTS

The Bioethics Commission is grateful to all those who contributed their time, insight, and expertise to this report. A wide-ranging group of exceptional speakers participated in our public meetings, shared their wisdom, and engaged in consistently productive and thought-provoking discussions. We greatly appreciate their public service.

The Bioethics Commission also thanks our talented staff for their dedicated support, careful research, and thoughtful insights on the ethics of pediatric medical countermeasure research. We extend our special thanks to Senior Advisor David DeGrazia for his important contributions to our deliberations and drafting, and to Executive Director Lisa M. Lee who has been a constant and thoughtful guiding force as the Bioethics Commission confronted a particularly challenging set of issues. The Bioethics Commission also is enormously grateful for the impeccable judgment and timely and tireless contributions of Associate Director Michelle Groman. We also extend great thanks to staff leads Kavita Berger, who led the project in its early phases, and Anne Pierson, who led it to completion, for their outstanding efforts on our behalf, which ensured a nuanced and thorough assessment of this weighty issue.

EXECUTIVE SUMMARY

Safeguarding children is one of our nation's foremost obligations. We have both a fundamental duty to protect individual children from undue risk during research and an obligation to protect all children during an emergency—to the extent ethically and practically possible—by being prepared both with the fruits of scientifically and ethically sound research and with a fulsome national readiness to respond.

In January 2012, the Secretary of Health and Human Services (HHS) asked the Presidential Commission for the Study of Bioethical Issues (the Bioethics Commission) to advise the U.S. government—in its mission to be fully prepared to mitigate the impact of bioterrorism attacks—on ethical considerations in evaluating and conducting pediatric medical countermeasure (MCM) research.¹ The Secretary also asked that the Bioethics Commission “include the ethical considerations in conducting a pre- and post-event study of [anthrax vaccine adsorbed (AVA) post-exposure prophylaxis] in children as part of its review.”²

Pediatric MCM research involves testing interventions with children that will be used in response to an attack either before an attack occurs (i.e., pre-event research) or testing such interventions following an attack (i.e., post-event research). Pre- and post-event pediatric MCM research poses risks to the individual children enrolled in research who, in many cases, do not stand to benefit directly from the research.

Research with children differs from that with adults because children cannot consent in the relevant sense; they are substantially lacking in the developed capacities necessary for adequately informed and voluntary decision making, making them a vulnerable population. Although this incapacity is most often attributed to their level of cognitive development, the vulnerability of children can derive from multiple sources (such as expectations of deference to adult authority, lack of independent resources for autonomous decision making, and longstanding institutionalized relationships of adult authority and power). For this reason, extra protections are warranted to ensure that children are not placed at excessive risk for the benefit of others. These additional safeguards include: parental permission, meaningful child assent, and limits on the degree of permissible research-related risk.

The Bioethics Commission's ethical analysis lies at the intersection of the unique characteristics of MCM research and pediatric research. In its 1977 report, *Research Involving Children*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) presciently described this type of challenge: "The ethical principles at stake are the moral obligation to protect the community... and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good."³

The four ethical principles that guides the Bioethics Commission's discussion of pediatric research protections are respect for persons, beneficence, and justice—as outlined in the *Belmont Report*⁴—and democratic deliberation, which was implicit both in the way the National Commission carried out its work and also in its recommendations regarding the process of reviewing and approving pediatric research.

HHS (and later the U.S. Food and Drug Administration (FDA)) adopted the National Commission's recommendations almost verbatim, and the regulations subsequently promulgated concerning research with children remain largely the same today, comprising Subpart D of HHS regulations at 45 C.F.R. Part 46 and FDA regulations at 21 C.F.R. Part 50.⁵

The National Commission's most straightforward recommendations addressed research that poses only minimal risk or that offers the prospect of direct benefit to participants. These recommendations would subsequently be codified in sections 404 and 405 of the HHS regulations. More complicated, but still ethically tractable, was research posing greater than minimal risk but likely to yield generalizable knowledge about the participants' condition. Research that is greater than minimal risk with no prospect of direct benefit to subjects or benefit to others with their condition was considered decidedly more controversial and ethically problematic. In the regulations, this last type of research was reserved for evaluation and approval by a national panel of experts and the Secretary of HHS for HHS-supported research (section 407).⁶

Pre-event Research

Pediatric research that presents no prospect of direct benefit to participants or that is not likely to yield generalizable knowledge about the participants' condition generally can only be conducted if it presents no more than minimal risk, except in extraordinary circumstances. Thus, the Bioethics Commission concluded that pre-event pediatric MCM research—which presents no prospect of direct benefit because no children are affected by the condition being studied—generally cannot proceed unless it is minimal risk research. Pre-event research might in some cases be designed in a way that would permit it to be judged minimal risk through an age de-escalation process in which risks are assessed and evaluated at each step. Robust research with young adults might support the conclusion that research with the oldest children is minimal risk. Similarly, research with the oldest children that further characterizes research risk might support an inference that research with the next oldest group of children is minimal risk as well.

Recommendation 1: Pre-event Pediatric Medical Countermeasure Research Risk Limited to Minimal Except under Extraordinary Circumstances

Pre-event pediatric medical countermeasure testing should be conducted with a research design posing only a minimal level of research risk except under extraordinary circumstances. If pre-event pediatric medical countermeasure research cannot be conducted as a minimal risk study, research that exposes children to no more than a minor increase over minimal risk—a level that is still very limited and poses no substantial risk to health or well-being—should proceed to a national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54.

Recommendation 2: Risk in Pre-event Pediatric Medical Countermeasure Research

Before beginning pre-event medical countermeasure studies with children, ethically sound modeling, testing with animals, and testing with the youngest adults must be completed to identify, understand, and characterize research risks. If pediatric research is determined to be minimal risk and is to be conducted, progressive age de-escalation should be employed whenever

possible from the oldest age group of children to the youngest group necessary to provide additional protection to the youngest and most vulnerable children, and to ensure that data from an older age group can inform the research design and the estimate of risk level for the next younger age group.

There will be instances in which it will be impossible to design minimal risk pre-event MCM research. In such cases, national-level review under section 407 would be required, but review should proceed only if researchers can demonstrate that the research poses no more than a minor increase over minimal risk to participants.

Recommendation 3: Pre-conditions to National-Level Review of Pre-event Pediatric Medical Countermeasure Research

Pre-event pediatric medical countermeasure research may proceed to national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54 only when researchers have demonstrated and reviewers concur that a minimal risk study is impossible and the proposed study poses no more than a minor increase over minimal risk to research participants. In part because of the inherent uncertainty of a bioterrorism attack, pre-event pediatric medical countermeasure research posing greater than a minor increase over minimal risk should not be approved under 45 C.F.R. § 46.407 or 21 C.F.R. § 50.54.

The Bioethics Commission's recommended framework, structured around the three conditions for national-level review, clarifies the circumstances in which proposed research presents a "reasonable opportunity" to address a "serious problem," specifies a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with "sound ethical principles," and reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent. Decision makers should assess proposed pre-event pediatric MCM research that poses more than minimal risk using this framework in order to ensure that all the necessary aspects of a study have been evaluated and found ethically permissible before moving forward.

Recommendation 4: Ethical Framework for National-Level Review of Pre-event Pediatric Medical Countermeasure Research

To ensure the thoroughness and ethical rigor of national-level review, reviewers should apply the Bioethics Commission’s recommended ethical framework for reviewing pre-event pediatric medical countermeasure research that poses greater than minimal risk, but no more than a minor increase over minimal risk, under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54. A proposed protocol must meet the requirements of the framework outlined in this report to be approved.

The framework clarifies the circumstances in which proposed research presents a “reasonable opportunity” to address a “serious problem,” in particular, that seriousness must be judged by the consequences of exposure, likelihood (or threat) of exposure, and the “vital importance” of the information to be gained. The framework also specifies a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with the required “sound ethical principles” that fall into five general categories: (1) ethical threshold of acceptable risk and adequate protection from harm; (2) ethical research design, for example, scientific necessity, valid research plan using small trials and age de-escalation with appropriate monitoring, and planning for post-event research; (3) post-trial requirements to ensure ethical distribution of medical countermeasures in the event of an attack, as well as a plan for treatment or compensation for research-related injury; (4) community engagement; and (5) transparency and accountability. Finally, the framework reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent.

Application to Trials of AVA with Children: Pre-event Research

In confronting the ethical questions surrounding MCM testing in pediatric populations, the Bioethics Commission concluded that before ethical pre-event pediatric AVA trials can be considered, further steps must be taken, including additional minimal risk research with adult participants to determine whether the research risks to children—who do not stand to benefit directly from it—pose no substantial risk to their health or well-being.

Given the amount of safety, immunogenicity, and dosing information about AVA in young adults aged 18 to 25 years, and given the widespread distribution of AVA in this population, it is possible that with additional testing in adults aged 18 to 20 years—testing to determine adverse effects, alternative dosing methods, and immunogenicity—testing of AVA with the oldest children (e.g., adolescents who are 16 to 17 years of age) could be considered no more than minimal risk. Consequently, it would be reviewed under section 404.

Informed, careful age de-escalation might allow researchers to infer minimal risk studies down the age scale. However, if data suggest that the use of AVA is affected, for example, by a child’s developmental stage (e.g., infancy or puberty), or if an inference of minimal risk from an older group of children to the next younger group is not possible, a study designed to pose a minor increase over minimal risk might be appropriate for national-level review.

Post-event Research

Public health officials must be prepared to conduct post-event research when a bioterrorism attack occurs regardless of whether pre-event pediatric MCM research trials were conducted. In contrast to pre-event testing, in which ethical deliberations focus on whether any research with children would be ethically permissible, in post-event circumstances, research is ethically required to safeguard the well-being of current and future children. If a pediatric MCM research trial were completed pre-event, data should be collected following the administration of the tested intervention to acquire necessary additional safety information. In the absence of a pre-event investigation, an emergency situation might warrant administering an untested MCM to children in an effort to save lives. When children receive an untested MCM, it is ethically imperative that health officials collect data to learn as much as possible about the use of the untested MCM from the event.

Recommendation 5: Post-event Pediatric Medical Countermeasure Research

Post-event research should be planned in advance and conducted when untested medical countermeasures are administered to children in an emergency or when limited pre-event medical countermeasure studies have already occurred. Institutional review boards must be cognizant of the exigencies imposed upon research under emergency conditions, and when reviewing

post-event medical countermeasure research proposals, ensure that adequate processes are in place for informed parental permission and meaningful child assent. Institutional review boards must also ensure that the research design is scientifically sound, children enrolled in research have access to the best available care, adequate plans are in place to treat or compensate children injured by research, and provisions are made to engage communities throughout the course of research.

In the event of a bioterrorism attack, the U.S. government has emergency preparedness plans to mobilize medical interventions, drugs, vaccines, and supplies from the Strategic National Stockpile for distribution to affected portions of the population. The federal government delivers supplies to the states, which have individualized distribution strategies based on localized need and infrastructure. In the event that the MCM needed is either still in clinical trials or has not yet been approved for the specified application, there are two mechanisms available—an emergency use authorization (EUA) and an investigational new drug application (IND)—that allow the government to distribute an unapproved intervention to help people in an emergency. Underlying the motivation for these mechanisms are a host of ethical principles including respect for persons, beneficence, and justice. Together, the EUA and IND provide mechanisms to supply necessary MCMs with varying levels of clinical and research protections to ensure adequate respect for persons, as appropriate.

Recommendation 6: Regulatory Mechanisms for Post-event Pediatric Medical Countermeasure Research and Distribution

When there are no data on the administration of a medical countermeasure to children and it will be provided to children in an emergency, the medical countermeasure should be provided under a treatment investigational new drug application (IND) to ensure that rigorous pediatric research protections apply to safeguard those children who receive the medical countermeasure. When a medical countermeasure is distributed broadly to children using a treatment IND, it is essential that the U.S. government also conduct a concurrent small-scale study under an investigator IND to obtain data that can potentially be used to support an emergency use authorization for pediatric use of the medical countermeasure in a future event. To expedite post-event research and ensure the availability of appropriate medical countermeasures

for children, a pre-IND consultation and approval should be put in place before an event.

Application to Trials of AVA with Children: Post-event Research

In an event involving the release of weaponized anthrax, or other large-scale release of spores, a plan exists to provide children, like adults, treatment with a 60-day course of antibiotics as well as AVA.⁷ FDA and the U.S. Centers for Disease Control and Prevention (CDC) have a treatment IND in place to allow for broad access to AVA for children in the event of an emergency. Work is ongoing to clarify the informed consent process. In addition, FDA and CDC are collaborating to develop a nested protocol that would involve research and surveillance to better understand immunogenicity and reactogenicity to the vaccine.⁸ Both of these mechanisms require IRB approval.

Under the Bioethics Commission's ethical approach, even if a pre-event study of AVA with children is approved, post-event research would be necessary to gather additional safety and immunogenicity data beyond the limited amount a pre-event study could produce. If a pre-event study is not approved and AVA is nonetheless administered to children in the event of an attack, post-event research would be ethically required.

It is important that any post-event distribution of AVA to children, regardless of the specific mechanism, entail democratic deliberation in the form of extensive community engagement. Community engagement should begin in pre-event research and continue through post-event activities. Moreover, it is critical that any post-event research protocol be scientifically sound, have adequate processes in place to ensure informed parental permission and meaningful child assent, provide for adequate treatment or compensation for research-related injuries, and ensure that enrolled children have access to the best available care.

* * *

Pediatric MCM research brings into sharp focus the fact that the health and security of children are paramount. It highlights the importance of both protecting children from unjustifiable research risks and assuring their safety as far as possible in the event of an emergency. Grounding its work in the principles of respect for persons, beneficence, justice, and democratic deliberation,

the Bioethics Commission reaffirmed the ethical foundations of pediatric research and applied them to the particularly complex and difficult case of pediatric MCM research. As exemplified by the Bioethics Commission's deliberations, such research warrants an ongoing national conversation in order to ensure the highest standards of protection for children that reflect an unwavering commitment to safeguard all children *from* unacceptable risks in research and *through* research that promotes their health and well-being.

CHAPTER 1

Introduction

Our sense of justice, beneficence, and respect for human dignity calls upon the country to do what it reasonably can to safeguard all children in the event of a public health emergency. This protection includes, for example, providing medicine, vaccines, and other interventions as needed. Our same sense of justice, beneficence, and respect for human dignity calls on us to safeguard individual children who participate in scientifically and ethically sound clinical research to develop these interventions and to protect individual children from participating in research that could impose undue risks on them. In other words, as a country, we have both a fundamental duty to protect individual children from undue risk during research and an obligation to protect all children during an emergency—to the extent ethically and practically possible—by being prepared both with the fruits of scientifically and ethically sound research and with a fulsome national readiness to respond.

In January 2012, the Secretary of Health and Human Services (HHS) asked the Presidential Commission for the Study of Bioethical Issues (the Bioethics Commission) to advise the U.S. government—in its mission to be fully prepared to mitigate the impact of bioterrorism attacks—on ethical considerations in evaluating and conducting pediatric medical countermeasure (MCM) research.⁹ Pediatric MCM research involves testing interventions with children that will be used in response to an attack either before it occurs (i.e., pre-event research) or testing such interventions following an attack (i.e., post-event research). Pre- and post-event pediatric MCM research pose risks to the individual children enrolled in research who, in many cases, do not stand to benefit directly from the research.

The tension between the need to conduct pediatric MCM research to protect children in the event of a future attack and the risks of this research to individual children who do not stand to directly benefit from it creates the central ethical challenge of pediatric MCM research. As noted in the *Belmont Report*, the ethical dilemma facing the Bioethics Commission derives in part from the principle of beneficence, which “requires that we protect against risk of harm to subjects and also that we be concerned about the loss of the substantial benefits that might be gained from research.”¹⁰ The Bioethics Commission addresses this tension in this report.

A major bioterrorism attack could require deployment of pediatric MCMs. To safeguard children in the event of a bioterrorism attack, MCMs should be ready and available for pediatric use. Under current federal plans, in the event of an emergency, children would be provided with at least some MCMs that have been approved for adults, even though many of these treatments have not been tested with children. Extrapolating from data in adult populations may be insufficient to determine safety and proper doses of MCMs for children. Pediatric research might therefore be necessary to determine the safest doses and formulations of MCMs for children.

Pre-event MCM research presents challenges that are distinct from other types of research, as it involves research on a hypothetical condition with an undefined (and perhaps unknowable) likelihood of occurring. And, while the knowledge gained could be profoundly useful, we may never have (and hope never to have) occasion to use it. The ramifications of these characteristics are discussed in greater detail below.¹¹

Post-event research poses its own challenges because this research generally will be conducted in very stressful circumstances. In post-event MCM research, the experimental intervention will often be provided in concert with additional tested treatments that could confound data collected regarding the MCM. Moreover, the stressful circumstances in which post-event research likely will be conducted might make safeguards such as obtaining adequate informed parental permission and meaningful child assent particularly difficult. In this report, the Bioethics Commission also addresses research conducted when the threat of an attack is imminent, because, as discussed in greater detail below, in these cases the ethical and practical concerns track those of a post-event study even if technically conducted pre-event.¹²

Pediatric research itself presents particular ethical complications. Competent adults can generally consent to accept risks for the benefit of others during research through the informed consent process. Agreeing to place oneself at risk for the good of others is often viewed as admirable, generous, and honorable. Children, on the other hand, are ethically and legally incompetent to consent on their own behalf, and therefore cannot agree to assume research risks for the benefit of others. A child's reduced autonomy and increased vulnerability, along with the inability to provide

informed consent, necessitates additional protections during research. These protections include limits on the level and types of research risks a child can be asked to assume, and generally require some prospect of direct benefit to the participant if research risks exceed the minimal ones that a healthy child living in a safe environment routinely encounters in daily life or during a routine medical examination.¹³

The Bioethics Commission’s ethical analysis lies at the intersection of the unique characteristics of MCM research and pediatric research. In its 1977

DISTINGUISHING COMMISSIONS

Presidential Commission for the Study of Bioethical Issues (the Bioethics Commission)

- 2009-present
- Established by Executive Order 13,521, President Barack Obama
- Scope: advise the President on bioethical issues that may emerge as a consequence of advances in biomedicine and related areas of science and technology

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission)

- 1974-1978
- Established by the National Research Act, 93rd Congress of the United States
- Scope: identify the basic ethical principles that should underlie the conduct of human subjects research and develop guidelines to govern such research

Sources: Executive Order No. 13,521, 74 Fed. Reg. 62,671 (Nov. 24, 2009); National Research Act of 1974, Pub. L. No. 93-348, 88 Stat. 342.

report, *Research Involving Children*, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission) presciently described this type of challenge: “The ethical principles at stake are the moral obligation to protect the community...and the moral prohibition against using unconsenting persons, at considerable risk to their well-being, for the promotion of the common good.”¹⁴

Although the National Commission did not address pediatric MCM research specifically, the principles it articulated—respect for persons, beneficence and its corollary, non-maleficence, and justice—offer a way to frame the complexities of MCM research involving children. An additional principle implicit in the National Commission’s work—democratic deliberation—further informs this analysis. For this report, the Bioethics Commission examined

these existing, well-established ethical principles that guide pediatric research to enumerate considerations for the ethical conduct of pre-event and post-event MCM studies with children.

The Bioethics Commission first considered pre-event studies: those posing minimal risk (i.e., no greater risk than that faced by a healthy child in daily life or at a routine medical examination) as well as those posing greater than minimal risk while offering no direct prospect of benefit to the individual child participants—but that are important to the potential future benefit of many or all children.¹⁵ The Bioethics Commission then considered post-event studies: those posing minimal risk as well as those posing some additional risk but also offering the prospect of direct benefit to the individual children who participate or offering the prospect of generalizable knowledge about the participants' condition. Both pre- and post-event MCM research studies with children are ethically challenging. For each of these categories, and consistent with its charge, the Bioethics Commission also examined the specific ethical issues raised in the context of proposed research on anthrax vaccine adsorbed (AVA) with children.

“Ethical issues about the involvement of children arise because of competing answers to the following question: Under what conditions (if any) are these various types of research justified?”

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1977). *Research Involving Children* (DHEW Publication OS 77-0004). Washington, DC: Department of Health, Education, and Welfare, p. 91. Retrieved from http://bioethics.georgetown.edu/pcbe/reports/past_commissions/Research_involving_children.pdf.

Anthrax Vaccine Adsorbed

The complexities of pediatric MCM research were highlighted by government action surrounding AVA, a particular MCM for anthrax. In early 2011, the U.S. government conducted an exercise called Dark Zephyr to test local, state, and federal government responses to a large-scale anthrax release in a major metropolitan area.¹⁶ Dark Zephyr revealed that about 7.6 million individuals would be exposed to anthrax during such an event, including as many as 1.7 million children, all of whom would require treatment. Although the government had plans in place to treat adults, officials involved in the exercise quickly realized that there was no evidence supporting a clear course of action for the treatment of children. The planned response during the exercise involved administering AVA for post-exposure prophylaxis to both

adults and children, in combination with antibiotics. The U.S. Food and Drug Administration (FDA) has approved AVA for use by adults before an anthrax exposure, but has not approved AVA for post-exposure prophylaxis by adults or for any use by children, and there are no data on the use of AVA by children. While antibiotics help prevent or treat immediate infection with anthrax—and are the only currently approved post-exposure treatment for children—they cannot provide the long-term protection that vaccination confers against the persistence of dormant spores.¹⁷ Long-term use of antibiotics is also associated with side effects, including gastrointestinal discomfort, which can result in intolerance and poor adherence. In addition, evidence from animal models suggests that even the initial response to combined antibiotic and vaccine treatment is superior to antibiotics alone.¹⁸

In the absence of data on the use of AVA by children, and the corresponding lack of FDA approval for its post-exposure use in pediatric populations, current HHS plans—based on recommendations by the Advisory Committee on Immunization Practices (ACIP)—include making available a three-dose course of AVA in combination with antibiotics to children who have been exposed to anthrax and conducting post-event observational research with a subgroup of those children who received it to better understand the effects of AVA.¹⁹ Research protections would be in place for all children receiving AVA—whether as treatment or as part of a research study. (See Authorizing Distribution of Unapproved Drugs in an Emergency, Chapter 3.)

Scientific Recommendation by the National Biodefense Science Board

In response to the findings of *Dark Zephyr*—in particular, the nation’s lack of preparedness to treat children in the event of an anthrax attack—Dr. Nicole Lurie, HHS Assistant Secretary for Preparedness and Response, asked the National Biodefense Science Board (NBSB) to recommend the “best course of action to prepare for a potential use of AVA vaccine in a pediatric population.”²⁰ In addition, Dr. Lurie requested that NBSB consider the risks involved in conducting a study of AVA with children before or after an attack and the logistical challenges of administering AVA to children during an attack.²¹

In its October 2011 report, NBSB considered whether to conduct pre-event research to gather safety and immunogenicity (degree of immune response) data about AVA with children, or whether instead to gather such data post-event. In conducting its analysis, NBSB accepted “the [U.S. government’s] threat analysis and recognize[d] that the dissemination of *B[acillus] anthracis* spores is a threat to the U.S. population, including its large proportion of children.”²² NBSB also explicitly stated that “administering AVA to children would present more than a minor increase over minimal risk” due specifically to the lack of data about AVA with children.²³ NBSB ultimately recommended that the U.S. government conduct a pre-event study to test the safety and immunogenicity of AVA with children before an anthrax attack occurs, but noted that any pre-event AVA study should proceed only following a thorough review of the ethical considerations involved.²⁴ This ethical review became part of the Bioethics Commission’s task outlined here, and NBSB’s scientific and technical assessment informed this ethical review.

The Bioethics Commission’s Charge

Catalyzed by NBSB’s recommendation, HHS Secretary Kathleen Sebelius asked the Bioethics Commission in January 2012 to “conduct a thorough review of the ethical considerations of conducting clinical trials of medical countermeasures in children,” and to “include the ethical considerations in conducting a pre- and post-event study of AVA [post-exposure prophylaxis] in children as part of its review.”²⁵

THE NATIONAL BIODEFENSE SCIENCE BOARD

The Pandemic and All-Hazards Preparedness Act established NBSB in 2006. The 13-member board advises the Secretary of HHS on “scientific, technical, and other matters of special interest” to HHS regarding activities to prevent, prepare for, and respond to adverse health effects of public health emergencies resulting from “chemical, biological, nuclear, and radiological events, whether naturally occurring, accidental, or deliberate.” NBSB members come from diverse backgrounds and a range of experience in both medicine and public health. The members are required to meet at least twice a year in a public forum.

NBSB has advised the Secretary on many issues, including: H1N1 immunization, home stockpiling of MCMs, mental health issues during a disaster, and prioritization in MCM development.

Source: Kathleen Sebelius, Secretary, HHS. (2012, July 3). National Biodefense Science Board Charter, p. 1. Retrieved from <http://www.phe.gov/Preparedness/legal/boards/nbsb/Documents/2012-renewed-charter.pdf>.

“Because of the sensitivity of the involvement of children in research, [NBSB’s] recommendation voiced [its] desire to have other focused experts, like [the Presidential Commission for the Study of Bioethical Issues], formally review and address these issues from an ethical perspective. ... The [NBSB] is confident that the [Bioethics] Commission will help us and our nation deliberate this very complex issue, ensuring safe medical countermeasures for our children.”

Parker, J.S., Chair, NBSB. (2012). The National Biodefense Science Board Report. Presentation to the Presidential Commission for the Study of Bioethical Issues, May 17. Retrieved from <http://bioethics.gov/cms/node/715>.

Although the Bioethics Commission’s charge stemmed from NBSB’s recommendation, the charge was significantly broader than a review of the ethical considerations associated with a pre-event pediatric study of AVA. As stated in Secretary Sebelius’s request, the Bioethics Commission was charged with considering the ethical issues associated with pediatric research for all MCMs; that is, drugs and vaccines intended to treat or prevent physical harm (or to diagnose a condition) resulting from a bioterrorism attack. The Bioethics Commission considered the term MCM to encompass all

FDA-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.²⁶

Ethical and Regulatory Framework for Pediatric Research

Pediatric research is critical for identifying safe and effective ways to diagnose, prevent, and treat disease and injury in children. Ethical pediatric research should minimize risks and, when possible, provide a reasonable prospect of direct benefit to individual participants. Unlike research with freely consenting adults, in which greater levels of risk might be permissible even without the prospect of direct benefit, children who participate in research are afforded special protections due to their vulnerability and inability to legally consent to participate. Any research conducted with children must therefore respect children’s well-being and dignity as persons, as well as their current and future capacities for self-determination, and must protect children from exploitation. These ethical imperatives are dictated by the foundational principles of respect for persons, beneficence (and its corollary non-maleficence), justice, and democratic deliberation.

The current regulatory framework adopts an approach recommended by the National Commission, that is, categorizing pediatric research based on both the level of research risk and the prospect of direct benefit to participants. Research that poses only minimal risk to participants, research that offers the prospect of direct benefit to participants, or research that provides the opportunity to gain generalizable knowledge about the participants' condition each fits neatly into one of the regulatory categories of research approvable at the local level, which are intended to govern the majority of pediatric research.²⁷

Some proposed MCM research, however, might involve exposing healthy children to greater than minimal risk while offering no prospect of direct benefit, and therefore does not fit into one of these categories.²⁸ In its report *Research Involving Children*, the National Commission recognized the ethical challenge inherent in considering whether research that poses more than minimal risk and offers no prospect of direct benefit to participants nevertheless might be justified by the “promise of substantial long-term benefit to children in general.”²⁹ The National Commission did not reach a conclusion about the permissibility of any such research with healthy children, instead recommending that decisions—taking into account “sound ethical principles” along with other important considerations—be made at the national level on a case-by-case basis. It intended this type of review only for rare and exceptional cases.³⁰

About this Report

This report by the Bioethics Commission enumerates the ethical considerations associated with conducting pre- and post-event MCM research with children. The Bioethics Commission examined the current ethical and regulatory framework to assess the types of ethically permissible pre- and post-event research. It built on the work of the National Commission to provide decision makers with the necessary ethical tools to assess whether research posing greater than minimal risk with no prospect of direct benefit to healthy child participants—the most ethically complex pre-event pediatric MCM research—can proceed. Fulfilling its charge, the Bioethics Commission applied its analysis to the particular case of AVA as well.

Due to the unique characteristics of pre-event MCM research—including uncertainty that the research results will ever be used—and the fact that

children are not legally or ethically competent to consent to participate in research, the Bioethics Commission concluded that greater than minimal risk pre-event research is ethically unacceptable if valuable information about an MCM could be obtained using a study design involving only minimal risk. If pre-event pediatric MCM research cannot be designed as minimal risk, the proposed research should pose no more than a minor increase over minimal risk and proceed to national-level review. Although the regulations might allow pediatric research that poses greater than a minor increase over minimal risk to be approved if it also meets ethical standards, the Bioethics Commission concluded that higher risk is unacceptable in the context of pre-event MCM research. Such research does not directly benefit the child participants, and the likelihood that the results of such research would benefit other children is unknown or unknowable.³¹

In accordance with its commitment to democratic deliberation and transparency, the Bioethics Commission held four public meetings to address the Secretary's request. Experts addressed a range of ethical, public health, scientific, medical, security, and regulatory issues associated with this report, providing a wide array of professional and institutional perspectives, including those from scientific and medical communities, non-profit organizations, and other individuals and groups. The Bioethics Commission published a request for information in the *Federal Register* and received almost 100 written responses. In the course of its work, the Bioethics Commission performed an in-depth review of relevant literature, and in its deliberations, took into account the relevant work of prior commissions, in particular, the National Commission's pathbreaking work in establishing pediatric research protections.

Based on the Bioethics Commission's detailed examination, Chapter 2 of this report provides an overview of the ethical foundations for pediatric research protections and the current regulatory structure governing pediatric research. Chapter 3 sets forth and analyzes the ethical issues associated with conducting pre-event and post-event MCM research with children, and applies this ethical analysis to the particular case of AVA.

CHAPTER 2
Current Ethical and Regulatory Framework
for Pediatric Research

Pediatric research is essential to ensure that children have access to therapies that are safe and effective. “Children are not just small adults.”³² They vary substantially from adults—and from other children of different ages—in the ways they process medicines, respond to interventions, and interact with their environment. Drug effects and toxicities, as well as immune responses to vaccines, are affected by the rapid growth and development in body size, weight, and organ function, as well as the metabolic processes that characterize childhood.³³ Children behave differently from adults as well, for example, they generally spend more time outdoors and put objects in their mouths when they are young, increasing their exposure to some environmental contaminants.³⁴ Given these differences, without specific data from pediatric research, health care providers often have inadequate information to accurately estimate dosages, formulations, and treatment regimens.

The pharmaceutical industry historically has had little incentive to conduct systematic clinical trials with children, even when those trials could have been conducted with minimal risk to individual children, because childhood is relatively short and most children are healthy.³⁵ The market for pediatric pharmaceuticals and other medical products is small and subdivided by stages of development, often making it difficult to enroll adequate numbers of appropriate participants necessary for rigorous trials.³⁶ As of 1997, studies showed that up to 80 percent of the drugs used by children had never been studied in pediatric populations for safety, dosing, or efficacy.³⁷

Beginning in the late 1990s, out of concern for protecting children *through* research rather than *from* research, Congress passed a series of laws to remedy the paucity of pediatric data by creating incentives for ethically sound pediatric clinical research. This legislation, including the Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003, provided extended market exclusivity for products tested with children and enabled the U.S. Food and Drug Administration (FDA) to request drug and biologic testing with pediatric populations.³⁸ These incentive programs have spurred pediatric research and provided data that contributed to an approximately 50 percent reduction in off-label use of drugs for children.³⁹ This is a vast improvement from the recent past, although the rate of off-label use still remains high.⁴⁰

HISTORICAL RESEARCH ABUSES

A convergence of research abuses influenced the move toward regulatory human subjects research protections developed in part by the National Commission in the 1970s and enacted by the Department of Health, Education, and Welfare (now HHS) in the late 1970s and early 1980s. Research abuses, including well-known cases such as Willowbrook, Tuskegee, and the Nazi atrocities, were historically important in moving toward regulation. Henry Beecher's publication of an article in the *New England Journal of Medicine*, which exposed 22 cases of human experimentation abuses, also motivated human subjects research regulation. Among the cases included in Beecher's publication was the Willowbrook study—research conducted with institutionalized and mentally handicapped children.

Sources: Beecher, H.K. (1966). Ethics in clinical research. *New England Journal of Medicine*, 274, 1354-1360; Jones, J. (1993). *Bad Blood: The Tuskegee Syphilis Experiment*. New York, NY: The Free Press; Lederer, S.E., and M.A. Grodin. (1994). Historical Overview: Pediatric Experimentation. In Grodin, M.A. and L.H. Glantz. (Eds.). *Children as Research Subjects* (pp. 1-25). New York, NY: Oxford University Press, pp. 15-19; Mellanby, K. (1947). Medical experiments on human beings in concentration camps in Nazi Germany. *British Medical Journal*, 1(4490), 148-150.

The current ethical and regulatory framework has proven largely capable of protecting children in the face of increasing pediatric research: promoting their welfare and enhancing research quality. Medical countermeasure (MCM) research, however, presents unique ethical challenges to the existing regulatory framework.

This chapter provides an overview of the ethical and regulatory framework for pediatric research. It begins with an overview of the ethical principles that form the foundation of current federal regulations governing pediatric research and concludes with a discussion of how those foundational principles animated the development and adoption of pediatric research protections.

Ethical Underpinnings: Guiding Principles

A core set of ethical principles provides the foundation for pediatric research protections. Reflecting a consensus on the ethical conduct of human subjects research, these ethical principles are drawn from the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research's

(the National Commission's) *Belmont Report*, and furthered by democratic deliberation, which the National Commission and subsequent commissions practiced in their work, and this Bioethics Commission explicitly adds as a critical principle for publicly accountable decision making.⁴¹

In *Research Involving Children*, the National Commission emphasized the importance of including children in research to interrupt what had become a long history of untested and harmful pediatric innovations. The National Commission recognized that in addition to protecting children from research risks, society ought to protect children through research. This need to ensure the safety of children was grounded in respect for persons and the inability of children to consent to research-related risks.

The National Commission's report clarified what became the United States' central tenet of pediatric research: pediatric research generally should be allowed only when such research exposes children to minimal risk. Minimal risk research entails a level of risk in which the degree and likelihood of harm is no greater than that faced by a healthy child in daily life or at a routine physical or psychological examination.⁴² Research risk can be greater than minimal only when the research offers the prospect of direct benefit to participants themselves or, if a minor increase above minimal risk, when research offers the prospect of benefit to others with the same condition.⁴³ Except in extraordinary circumstances, asking children to take on greater risk in research when they do not stand to benefit directly pushes the bounds of ethical acceptability because children do not have the legal or ethical capacity to consent, and society has a duty to protect children from risk of harm to which they cannot consent. This view is widely shared, affirmed in leading international guidance documents, and reflected in U.S. law.⁴⁴ It continues to serve as the first principle of ethically sound pediatric research around the world today.

Development of the Central Tenet of Pediatric Research

The four ethical principles that guided the Bioethics Commission's discussion of pediatric research protections are respect for persons, beneficence, and justice—as outlined in the *Belmont Report*—and democratic deliberation, which was implicit both in the way the National Commission carried out its work and also in its recommendations regarding the process of reviewing and approving pediatric research.

Respect for Persons

The *Belmont Report* delineates the principle of respect for persons, which recognizes persons as autonomous and capable of deliberating about their

personal goals, considering their own choices and opinions, and determining their own lives. Respect for persons also establishes “that persons with diminished autonomy [including children] are entitled to protection.”⁴⁵ Some commentators believe that the obligation of “protection” in the *Belmont Report* is really a matter of beneficence.⁴⁶ However, disregard for the well-being of children also reflects a lack of respect owed to them as young persons. This respect derives in part from the fact that children have and will further develop personal values and goals, as well as the capacity for self-determination to strive and fulfill them.

Respect for persons requires that research participants with full decision making capacity be given the information and the opportunity to consent voluntarily and knowingly to what will happen to them as a result of their participation. This imperative is often viewed as deriving from the human capacity for reason and self-determination. Human beings are generally capable of setting their own ends in accordance with their values and priorities and rationally pursuing these ends. Treating others in a way that disregards their human capacity for rationality and self-determination constitutes disrespect for those persons, and when we use people only to pursue the ends or interests of others—in other words, using them as mere means—we fail to respect their human dignity. Coercive uses of research participants—as in the Nazi medical atrocities—provide the most obvious instances of the impermissible treatment of participants as means only.⁴⁷ Coercion of adult participants in research is a violation of a participant’s autonomy: the rational ability to direct the course of one’s own life.

To treat people *merely* as means—to exploit them or use them only to further the interests of others—is not the same as treating people both as means *and* as ends-in-themselves. Ethical human subjects research illustrates this distinction. Participation in research that offers a prospect of direct benefit might prove useful to others while simultaneously advancing the interests of individual research participants. In other instances of scientifically and ethically sound research, adult research participants are well informed and willing to bear personal risks with no expectation of return in order to benefit others. In these cases, transparency about risks and benefits allows individuals to make their own assessment of whether research participation comports with their personal values and pursuits. Accordingly, adults who provide their informed

consent to participate in otherwise scientifically sound and necessary research are not treated only as means, but also as ends in themselves.

Ethical Safeguards in Pediatric Research Informed by Respect for Persons

Research with children differs from that with adults because children cannot consent in the relevant sense; they are substantially lacking in the developed capacities necessary for adequately informed and voluntary decision making, making them a vulnerable population. Although this incapacity is most often attributed to their level of cognitive development, the vulnerability of children can derive from multiple sources (such as expectations of deference to adult authority, lack of independent resources for autonomous decision making, and longstanding institutionalized relationships of adult authority and power).⁴⁸ For this reason, extra protections are warranted to ensure that children are not placed at excessive risk for the benefit of others. These additional safeguards include: parental permission, meaningful child assent, and limits on the degree of permissible research-related risk.

Parental Permission. Parental permission requires that parents act on their child's behalf, operating on their understanding of what is in their child's best or essential interests.⁴⁹ With this in mind, parents might allow a child to participate in research that offers a prospect of direct benefit precisely because enrollment appears to promote the child's interests. In the context of research that poses no substantial risk to a child's health or well-being but offers no prospect of direct benefit, some parents will compare short-term risks and benefits. For these parents, research that provides no direct

APPLIED ETHICS IN PEDIATRIC RESEARCH

Paternalism constitutes those actions that restrict the freedom of others on the grounds that those actions are the best way to promote or protect their interests. In the case of children, such restrictions are not only justified because children cannot identify and pursue their own interests, but because "such restrictions on a child's freedom *guarantee his autonomy* in either or both of two ways: these restrictions protect the child from harm that would limit his freedom in the future (being seriously injured, or a lack of education), or these restrictions are what we think the child will *later* agree to, what he will later see as something he would do in his own interest."

Source: Redmon, R.B. (1986). How children can be respected as 'ends' yet still be used as subjects in non-therapeutic research. *Journal of Medical Ethics*, 12(2), 80. [Original emphasis].

benefit might be out of the question. Other parents might be willing to take on risk for themselves but reluctant to subject their child to any research risk without the prospect of direct benefit—not knowing what the child will think (upon reaching adulthood) about having been subjected to risk for the benefit of others without their consent. And still other parents will give greater weight to the study’s incremental contribution to long-term scientific or societal endeavors, which might eventually result in medical progress that helps their child or the child’s potential offspring, as well as other children. Alternatively, parents might enroll their children in research that poses no substantial risk to their health or well-being to teach them a moral lesson about the value of service to others. Parents of older children might wish to give effect to their developing autonomy by including them in projects to which they assent and which they might later endorse as consistent with their own ethical perspective and interests.⁵⁰

Meaningful Child Assent. While children are not fully autonomous, they nevertheless have varying capacities to make informed, self-regarding choices and express their preferences regarding how they will be treated. Children’s partial autonomy affords them a developmentally appropriate ability to participate in decisions regarding their involvement in research. Out of respect for this developing ability of children, their assent should be solicited, if possible, and their dissent respected, if applicable.⁵¹ Obtaining the meaningful assent of a capable child is one component of respecting that child as a person. It must not be interpreted, however, either as informed consent or as a substitute for parental permission. Parental permission is absolutely necessary to informed participation in conjunction with meaningful child assent.

The fact that children have a developing capacity for autonomy lends significance to a child’s meaningful assent or dissent and also establishes a need to protect this capacity for self-determination. The principle of respect for persons permits only those research protocols that preserve and sustain the full development of a child’s autonomy, such that the current and future aspirations of some children are never unduly compromised merely for the sake of benefitting others. This is accomplished in important part by the final form of protection discussed here, which limits the degree of risk to which children can be exposed in research.

Limiting the Degree of Research-Related Risk. Placing strict limits on the level of risk acceptable in pediatric research is a third and critically important way to protect children in light of their incomplete autonomy and their inability to consent. Child research participants will one day grow up and reflect on whether they would have consented to participate in the research, had they been capable. While parents may exercise legitimate discretion when granting permission for their children to enroll in research, there is no way to know whether all participants, once adults, will endorse the decision retrospectively (even if they provided meaningful assent as children).⁵² To reduce the possibility that some participants will look back and think they were unethically used by their parents or researchers, protections should be in place to ensure that participants who reflect on their past research participation will be likely to endorse the ways in which they were protected, if not their own participation. On this view, past participants might later reflect that even if they would not have consented to participate, protections were in place that prevented them from being harmed.

Risk limits are essential to combat the potential for exploitation (of both children and adults), however unintended such exploitation may be. Because children cannot make an autonomous decision to participate in research, from an ethical and legal perspective, great care must be taken to ensure that research risks are rigorously limited. In particular, because research is, in part, always justified on the basis of potential benefit to others—but not necessarily to the children who are subject to risks as research subjects—special efforts must be made to ensure that children are not exploited by permitting greater research risks to children when society stands to benefit in greater measure.⁵³ The imposition of a rigorous risk ceiling ensures that, no matter how great the potential benefit, child research participants are not exposed to a disrespectful and exploitative level of risk for the interests of others in society.

Another reason why it is important to limit the research risks to which children are subjected is that the state does not have the same broad latitude as parents to make risk-laden decisions on behalf of children. There are public obligations to limit both the outer bounds of parental authority (so as to prevent negligence) and the outer bounds of governmental authority over children (so as to prevent the exploitation of individual children for public purposes). One way in which the government defines the outer bounds of its

own authority over individual children and respects the future autonomy of children is by limiting the levels of research risk that parents may be asked to accept for their children, especially when that research is above minimal risk and does not directly benefit the child. These risk limits are one of the core protections that children receive both out of respect for their dignity as persons and to help ensure that they will be able to exercise their own autonomy as adults.

Interpreting the Scope of Respect for Persons

Given that children are allowed, under clearly delineated circumstances, to participate in research without the prospect of direct benefit, current regulations implicitly reject one particularly restrictive interpretation of the principle of respect for persons. (See Current Regulations for Conducting Pediatric Research, Chapter 2.) Under this most restrictive interpretation, due to their incapacity to consent, the principle of respect for persons would prohibit all research with children (including even minimal risk research) that offers no prospect of direct benefit.⁵⁴ Strong consensus in the field of bioethics—including the judgment reflected in the National Commission’s position—regards this understanding as overly restrictive. An alternative, widely accepted interpretation of respect for persons allows for the participation of children in research that offers no prospect of direct benefit under certain carefully defined circumstances—even if the research imposes more than minimal risk on pediatric participants, stopping short of posing any substantial risk to the fundamental health or well-being of the research participants. On this widely accepted interpretation, research without the prospect of direct benefit is permissible if it imposes no greater than minimal risk—a level of risk comparable to the risks that healthy children living in a safe environment routinely encounter in everyday life or during a routine medical examination—and, under certain limited circumstances, a slightly higher (but still very limited) level of risk, which poses no substantial risk to the participants’ health or well-being.⁵⁵

The widely accepted interpretation of the principle of respect for persons should be endorsed on the grounds that research protections can help to ensure respect for children by safeguarding their current capacities, guaranteeing their future autonomy (by ensuring they are not treated as mere

means), and by not subjecting them to undue risk. In addition, this more inclusive interpretation receives support from other relevant moral principles. The principle of beneficence, further addressed in the next section, calls upon society and the research community to advance biomedical knowledge in the interest of the public's welfare. The importance of beneficence in the context of pediatric biomedical research counsels against the most restrictive interpretation of respect for persons and in favor of the widely accepted approach to pediatric ethics, as reflected in the National Commission's recommendations and current regulations.

* * *

All pediatric research must satisfy the ethical principle of respect for persons. This Bioethics Commission articulated a set of conditions under which pediatric research without the prospect of direct benefit fully respects and ethically protects children as individuals and as a group. (See *Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407, Chapter 3.*) By treating the interests of child participants as a paramount concern, pediatric research without the prospect of direct benefit can respect and uphold the humanity of participants, and refuse to view them as objects merely serving the ends of science or society, provided that the research risks are strictly limited and parental permission and meaningful child assent are obtained. This generally entails permitting research that involves no more than minimal risk, but under certain strictly limited circumstances, permitting a slightly higher than minimal (but still very limited) level of risk, provided that the protocol poses no substantial risk to the children's health or well-being.

Beneficence

Beneficence, as described in the *Belmont Report*, is the obligation to undertake efforts to secure the well-being of others. In pediatric research, the duty to safeguard participants by protecting them from harm and undue risk of harm is particularly salient because children have reduced autonomy and cannot legally consent, making them a vulnerable population.⁵⁶ Beneficence requires that special safeguards be employed to protect vulnerable populations (e.g., the requirement of minimal risk or prospect of direct benefit for most pediatric research). This principle provides additional support for the conclusion

that some proposed pediatric trials impose excessive risks, too high to ask parents to consider having their children bear. These studies would involve potential harm that would threaten the basic health or well-being of children who, as research participants, would not stand to directly benefit or be able to offer their own informed consent.

The *Belmont Report* includes under beneficence the corollary principle of non-maleficence, or “do no harm,” an obligation not to cause deliberate harm to others.⁵⁷ This obligation to minimize the risk of harm from research—especially for children in view of their inability to consent—provides an additional principled foundation for a firm limit to acceptable research risks. Notably, however, there might be cases in which, in order to avoid harm, research is needed to discover what is harmful. Similarly, to discover what is beneficial might, at times, require exposing some persons to the risk of harm. As stated by the National Commission, “The problem posed by these imperatives is to decide when it is justifiable to seek certain benefits despite the risks involved, and when the benefits should be foregone because of the risks.”⁵⁸

Beneficence is directed not only at individual research participants, but also toward the broader public, seeking to benefit society as a whole. The *Belmont Report* acknowledged this, stating, “The obligations of beneficence affect both individual investigators and society at large, because they extend both to particular research projects and to the entire enterprise of research.... In the case of scientific research in general, members of the larger society are obliged to recognize the longer term benefits and risks that may result from the improvement of knowledge and from the development of novel medical, psychotherapeutic, and social procedures.”⁵⁹ Those who deliberate and consider whether research should proceed ought to take into account the duty “of a society and its government to promote individual activities and institutional practices, including scientific and biomedical research, that have great potential to improve the public’s well-being.”⁶⁰

Beneficence guides the risk-benefit assessment in research. While “risk” indicates possible harm, “benefit” refers to the anticipated gains resulting from the research. The *Belmont Report* offered five considerations for assessing the risk-benefit justification in research with all human participants:

- i. Brutal or inhumane treatment of human subjects is never morally justified.

- ii. Risks should be reduced to those necessary to achieve the research objective.... Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures.
- iii. When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or, in some rare cases, to the manifest voluntariness of the participation).
- iv. When vulnerable populations are involved in research, the appropriateness of involving them should itself be demonstrated. A number of variables go into such judgments, including the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits.
- v. Relevant risks and benefits must be thoroughly arrayed...in the informed consent process.⁶¹

Two of these considerations are especially applicable to the question before this Bioethics Commission: (ii) reducing risk to that necessary to achieve the research objective and to the lowest possible level by considering alternative approaches; and (iv) justifying the appropriateness of including vulnerable populations, in this case children. Non-maleficence, which requires us to reduce research risks as far as possible, becomes especially salient when research is planned with children who cannot consent to assume risks on the behalf of others.

Beneficence and non-maleficence—similar to respect for children as persons—obligate us to ensure that research risks be necessary and minimized, and to employ alternative approaches that might avoid exposing children to risk—for example, using computer and animal models or adult participants who can consent to assume risk on behalf of others. Moreover, risks should be shown to be minimal in the youngest adults through testing them before proceeding with the oldest children. Further, non-maleficence toward child research participants and beneficence toward participants and toward society as a whole must be jointly considered in determining an acceptable level of risk. In general, research-related risks that are greater than minimal are ethically permissible only if there is a prospect of direct benefit for the child participants or there is the prospect of benefit to the class of children from which the participants are drawn.

Justice

The principle of justice reflects the National Commission's commitment to "‘fairness in distribution’ or ‘what is deserved.’"⁶² Ethical distribution of research burdens and benefits generally prevents the possibility of asking participants and families to consider bearing too heavy a burden on behalf of society. More specifically, in the conduct of research, justice requires that research participants not be denied a benefit to which they are entitled and that no individual participant be burdened with undue risk of harm or hardship. These obligations can be met by ensuring that all research participants are treated equitably—for instance, by allocating research burdens and benefits according to ethically justifiable criteria.⁶³ In the case of research with children, moreover, justice—in combination with respect for persons, beneficence, and non-maleficence—requires that children should not bear more risk than absolutely necessary during research, and that risks children undertake during research may be assumed only in order to address research questions that can only be addressed with children. For example, children should not be asked to bear research risks solely to benefit adults.

Just distribution of research risks applies not only to the design and conduct of research, but also to subject selection. Even when they are treated equitably once enrolled in research, children and families might be selected unjustly if they are chosen from certain subgroups of the population that are already excessively burdened by conditions of socioeconomic disadvantage, that have made uncommon sacrifices in the course of public service, or that have been subject to repeated recruitment for research enrollment. Reviewers and researchers must ensure that all necessary safeguards are in place to avoid exploiting participants when enrolling those who might be vulnerable based on their age, clinical status, marginalization, economic deprivation, or similarly relevant factors.⁶⁴ Just as justice requires that similar cases be treated similarly, so too does justice require that we be alert to significant differences. Researchers, therefore, must be cognizant of the potential for exploitation—the ability to take unfair advantage of participant vulnerability. The principle of justice requires, as noted by the National Commission, that researchers adapt their practices to treat cases that differ in "morally relevant respects" differently—for example, modifying consent or recruitment practices—in order to equalize protection from harm for all participants.⁶⁵

Once research has concluded, justice requires equitable distribution of benefits that emerge from successful research endeavors. Just distribution takes into account not only such factors as who participated in the research, but also ensures that children are not excluded from receiving benefits on the basis of poverty or other marginalizing factors.

Democratic Deliberation

Democratic deliberation is a process that seeks to clarify and articulate factual and ethical issues at the core of a debate, to create consensus whenever possible, and to map the terrain of disagreements in a respectful way—when agreement is not immediately attainable—by encouraging reciprocity, respect for persons, transparency, publicity, and accountability.⁶⁶ This principle embraces inclusion of community members—individuals and their representatives—in meaningful and active participation in an ongoing public exchange of ideas. In research, democratic deliberation is manifest, for example, in community engagement and in various aspects of institutional research review and approval.

The National Commission valued the principle of democratic deliberation and honored it both in its approach as well as its recommendations. While studying the matter of research protections for child participants in the 1970s, the National Commission took extensive measures to involve experts, advocates, parents, and other stakeholders. The National Commission invited representatives of professional societies, federal agencies, public interest groups, parents, and other members of the public to present their views at public hearings.⁶⁷ In addition to creating an open forum for interested individuals and parties to present their views, the National Commission actively convened a National Minority Conference on Human Experimentation to represent the views of those who might not otherwise be adequately represented.⁶⁸ The National Commission reviewed papers and surveyed existing pediatric research practices to inform its public deliberations and develop recommendations for pediatric research.

This inclusive approach to its deliberations was evident not only in the National Commission's process but also in the content of its report, *Research Involving Children*, which lays out its argument through chapters devoted to each level of its inquiry. These chapters include the various surveys to characterize

contemporary research, review, and consent practices; views presented by stakeholders; and discourse by psychology, law, and ethics experts of the day.⁶⁹

One recommendation in particular demonstrates the importance of democratic deliberation to the National Commission, not only in its own work but also in the ongoing review and approval of research with children. Although all pediatric research requires review by an Institutional Review Board (IRB)—a form of democratic deliberation—the National Commission recommended that research involving greater than minimal risk with no prospect of direct benefit to healthy children should only be approved after an opportunity for extensive public comment and open deliberation. Because the National Commission considered this category of research approvable only in extraordinary circumstances and as a matter of societal exigency, it considered soliciting the input of citizens essential both to inform and legitimate the work.⁷⁰

Accordingly, the National Commission recommended that research in this category could only be considered for approval by the Secretary of the responsible agency after consultation with a panel of experts and opportunity for public comment. Observing the principles at stake—(1) the obligation to protect the community or come to the aid of those within it, and (2) the prohibition against unethically using persons who cannot consent, at considerable risk to their well-being, for the common good—the National Commission stated, “[t]hese principles are of such moment and their observance so basic to a just and humane society that any debate about their application should be held at the most public level of discourse.”⁷¹

This Bioethics Commission reaffirms its own commitment to the principle and practice of democratic deliberation and its importance in shaping pediatric research protections. Given the dual obligations to protect individual research participants and to protect children as a class, enhanced transparency and accountability and extensive community engagement, for example, are essential to informing the review and conduct of pediatric research. By fostering meaningful inclusion of the affected communities at all stages of the research process, community engagement constitutes a component of democratic deliberation that researchers can employ to incorporate the values of the community into the research process. The Bioethics Commission includes in its recommendations appropriate provision for community

engagement in both pre- and post-event research.⁷² Moreover, in all stages of pediatric research, democratic deliberation provides an essential means of confirming both that the research is consistent with societal and community values and also that it achieves socially valuable—and broadly valued—goals. Indeed, the Bioethics Commission has begun the community engagement process specifically—and the democratic deliberation process more generally—through its deliberations, and recognized that communities are well-positioned to contribute to the discussion now, before any research occurs. A significant test of the social value and importance of pediatric research projects—especially when such projects subject individual children to some risk for the potential benefit of children as a class—is that a broad range of citizens and parents, having been informed and given the opportunity to comment, value and support those projects.

* * *

Foundational ethical principles provide both clarification and guidance in formulating strong safeguards for children, both as individuals and as a group. Essential research protections that follow from a principled approach often involve appeal to more than one ethical principle. One protection central to this report—a commitment to repudiating exploitation—provides a clear example of such an appeal. This commitment derives from the principle of respect for persons and its attendant imperative not to treat others as mere means as well as from non-maleficence (the duty to “do no harm”). The commitment to avoid exploiting the vulnerable is clearly a matter of justice, and deliberative democracy helps to assure a just outcome by promoting dialogue with those who have not yet had their chance to voice concerns, thereby protecting against exploitation.

Continuing in the tradition of the National Commission, this Bioethics Commission reaffirmed the view that ethical research is not research that strikes the appropriate “balance” or “trade-off” among fundamental social values, but rather “that all of these principles must be taken together as the necessary and sufficient conditions for the ethical conduct of research regarding children. Unless research can be designed which reflects all [four], it cannot be called ethical.”⁷³ The recommendations of this report therefore are informed by and seek to satisfy all four fundamental principles of respect for

persons, beneficence, justice, and democratic deliberation, which are widely affirmed by our society and firmly established in the best practices of scientific research with human subjects.

Current Regulations for Conducting Pediatric Research

The three Belmont principles and the principle of democratic deliberation also informed the National Commission's reasoning and recommendations for additional regulatory protections for pediatric research participants. The Department of Health and Human Services (HHS) (and later FDA) adopted the National Commission's recommendations almost verbatim, and the regulations subsequently promulgated concerning research with children remain largely the same today, comprising Subpart D of HHS regulations at 45 C.F.R. Part 46 and FDA regulations at 21 C.F.R. Part 50.⁷⁴ The language of these two sets of regulations is substantively identical. Although Subpart D makes up part of these agencies' human subjects protections regulations, it is separate from and supplementary to Subpart A, referred to as the Common Rule—which governs research with adults.⁷⁵ Subpart D specifies stringent protections for children in addition to those provided in the Common Rule.⁷⁶

The key impetus for a separate regulatory subpart addressing additional protections for child participants in research was the recognition that, while adults can consent to assume research risks, children cannot. More specific to the content of this report, adults can consent to participate in research from which they will accrue no benefit for themselves but that benefits others. By contrast, children cannot participate in research that poses higher risks than those of daily life, except in circumstances where research offers the prospect of benefit to participants themselves or to those with the same condition.

For the most part, protections for pediatric research participants are well defined and well implemented. The regulations include special protections for wards of the state, delineate requirements for parental permission and child assent, and provide criteria for IRBs to use in reviewing research depending on its level of risk and potential benefit.⁷⁷ Local IRBs can review and approve research with children that: (1) does not involve greater than minimal risk; (2) involves greater than minimal risk but presents the prospect of direct benefit to individual participants; or (3) involves a minor increase over minimal risk and no prospect of direct benefit to individual research participants, but is likely

**Table 2.1
Regulations Governing Review of Pediatric Human Subjects Research Protocols**

Local IRB Review Mechanisms

<p>45 C.F.R. § 46.404 Reflected by FDA at: 21 C.F.R. § 50.51</p>	<p>Minimal risk HHS will conduct or fund research in which the IRB finds that no greater than minimal risk to children is presented, only if the IRB finds that adequate provisions are made for soliciting assent of the children and the permission of their parents or guardians as set forth in § 46.408.</p>
<p>45 C.F.R. § 46.405 Reflected by FDA at: 21 C.F.R. § 50.52</p>	<p>Prospect of direct benefit to the individual participant HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject's well-being, only if the IRB finds that:</p> <ol style="list-style-type: none"> The risk is justified by the anticipated benefit to the subjects; The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.
<p>45 C.F.R. § 46.406 Reflected by FDA at: 21 C.F.R. § 50.53</p>	<p>Likely to yield generalizable knowledge about participants' condition and only minor increase over minimal risk HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds that:</p> <ol style="list-style-type: none"> The risk represents a minor increase over minimal risk; The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition; and Adequate provisions are made for soliciting assent of the children and permission of their parents or guardians, as set forth in § 46.408.

National-Level Review Mechanisms

<p>45 C.F.R. § 46.407 Reflected by FDA at: 21 C.F.R. § 50.54</p>	<p>Greater than minimal risk with no prospect of direct benefit to individual participants or those participants' condition HHS will conduct or fund research that the IRB does not believe meets the requirements of § 46.404, § 46.405, or § 46.406 only if:</p> <ol style="list-style-type: none"> The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and The Secretary,* after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either: <ol style="list-style-type: none"> That the research in fact satisfies the conditions of § 46.404, § 46.405, or § 46.406, as applicable, or The following: <ol style="list-style-type: none"> The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; The research will be conducted in accordance with sound ethical principles; and Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians, as set forth in § 46.408.
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* Note: In the case of review by FDA under § 50.54, the Commissioner of Food and Drugs convenes the expert panel and makes the final determination, which is forwarded to the HHS Secretary. For concurrent review under §§ 46.407 and 50.54, the Secretary makes the final determination.

to yield generalizable knowledge about the children's disorder or condition.⁷⁸ Local IRBs are not permitted to approve research outside of these categories, but "research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children"—generally higher risk, non-therapeutic research—can nonetheless be approved by the Secretary of HHS in consultation with a panel of national experts.⁷⁹ This report refers to such national-level expert review by its HHS provision number—45 C.F.R. § 46.407 (section 407)—which is a common convention in ethics discourse on this subject.⁸⁰ Equivalent substantive requirements are found in FDA regulations at 21 C.F.R. § 50.54. Whether the review is conducted by the HHS Office for Human Research Protection (OHRP), or FDA, or both, the ethical requirements are essentially the same across both sets of regulations.⁸¹ The regulations governing these review mechanisms are included in Table 2.1.

This report references research regulated by section 407 as research with healthy children that poses more than minimal risk with no prospect of direct benefit. The Bioethics Commission recognized and considered in its work the full range of research that is encompassed by section 407, including (1) research with healthy children that poses greater than minimal risk and that offers no prospect of direct benefit, (2) research with children affected by a disease or condition that poses more than minimal risk and does not yield information of vital importance about their disease or condition, and (3) research with children affected by a disease or condition that poses greater than a minor increase over minimal risk.

Pediatric Research Subject to Local IRB Approval

The National Commission's most straightforward recommendations addressed research that poses only minimal risk (codified in section 404) or that offers the prospect of direct benefit to participants (codified in section 405).⁸² More complicated, but still ethically tractable, was research posing greater than minimal risk but likely to yield generalizable knowledge about the participants' condition (codified in section 406).⁸³ Research that is greater than minimal risk with no prospect of direct benefit to subjects or benefit to others with their condition was considered decidedly more controversial and ethically problematic.

Section 404: Minimal Risk Research

Making its recommendation on minimal risk research, the National Commission recognized that “the scope of parental responsibility includes the right to choose activities and to define a manner of life for their children.”⁸⁴ Finding that “many experiences which parents generally allow to their children are somewhat risky and cannot be said, without forcing the case, to involve particular benefits,” the National Commission considered it uncontroversial that parents should have the opportunity to enroll their children in research where the risks “are equivalent to normal risks of childhood.”⁸⁵ The National Commission recommended and the regulations allow an IRB to approve minimal risk research that provides for parental permission and meaningful assent from child participants as well as standard pediatric research safeguards such as risk minimization, privacy and confidentiality protections, and equitable subject selection.⁸⁶ The National Commission defined minimal risk as “the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”⁸⁷

As implemented, protections for minimal risk research have been subject to ongoing debate—mostly focused on the regulatory definition of “minimal risk,” which omits the National Commission’s reference to healthy children. While disagreement remains as to whether the standard is intended to be objective or subjective, several national committees studying the matter have concluded that “minimal risk” should be interpreted as the degree of risk encountered in the daily life of a healthy child living in a safe environment or the risk to which a healthy child is exposed during a routine examination.⁸⁸ The Bioethics Commission accepted this shared understanding.

Section 405: Research Presenting the Prospect of Direct Benefit

In considering research that presents greater than minimal risk but also the prospect of direct benefit to research participants, the National Commission concluded that risk might be justified by “avoidance of greater harm” or provision of “important anticipated benefit.”⁸⁹ Any risk entailed in research, however, can be justified only by the potential direct benefits to the individual child participant that are associated with the intervention itself (not by ancillary benefits such as a medical examination). The risk-benefit

ratio of the experimental intervention must be at least as good as that of available alternatives.⁹⁰

The relevant regulatory language closely reflects that of the National Commission, stating that an IRB may approve a protocol if it finds that the risk is greater than minimal but that the research holds the prospect of direct benefit to the individual either through the intervention or through “a monitoring procedure that is likely to contribute to the subject’s well-being.”⁹¹ Beneficial monitoring procedures might include, for example, obtaining samples of blood or spinal fluid in order to determine that drug levels are safe and effective. A reviewing IRB must also find that (a) “[t]he risk is justified by the anticipated benefit to the subject[,]” (b) the risk-benefit ratio is at least as good as existing alternatives, and (c) all relevant parental permission and meaningful child assent provisions are observed.⁹² There is ongoing debate over the extent to which “benefit” should include non-medical benefits, but in practice, the scope is most often limited to medical benefits associated with the intervention being studied.⁹³

Section 406: More Than Minimal Risk Without the Prospect of Direct Benefit but Likely to Yield Knowledge About the Participants’ Condition

The National Commission recognized that some valuable research involving children will inevitably present greater than minimal risk with no prospect of direct benefit to the individual participants. Prohibiting this type of research completely, as initially supported by some members of the National Commission, might have come at too great a cost, sacrificing research of critical importance to child welfare in order to avoid “only a minor” increased risk.⁹⁴ In developing its recommendations for approval of a limited class of research entailing greater than minimal risk and no prospect of direct benefit, the National Commission kept in mind the proposition that parents are routinely allowed to authorize their child’s involvement in activities, such as skiing, where risk is greater than minimal and the potential for benefit is debatable.⁹⁵ Given that information, the National Commission recommended that pediatric research with no prospect of direct benefit and presenting no more than “a minor increase over minimal risk” could be ethically permissible and allowed by regulation if the knowledge likely to be generated by the research was of “vital importance” to understand or ameliorate a pediatric disorder or condition.

Specifically, in light of reports that valuable diagnostic, therapeutic, and preventive measures have been discovered in research that entails risk that “while minor, would be considered more than minimal,” the National Commission recommended that local IRBs could approve research that meets the following conditions: (1) “the risk involved must be only a minor increment beyond minimal,” (2) “the procedures to be used must be reasonably commensurate with (similar to) those with which prospective subjects have had experience,” and (3) “the research must be likely to yield generalizable knowledge important for the understanding or amelioration of the subjects’ specific disorder or condition.”⁹⁶ Research that meets these specifications may be approved because the minor additional increment of risk to participants is acceptable in light of the “foreseeable benefit in the future to an identifiable class of children.”⁹⁷

In making its recommendation, the National Commission emphasized that “minor increase over minimal risk” is only a “narrow” expansion and that any protocol submitted under this provision should “pose[] no significant threat to the child’s health or well-being.”⁹⁸ HHS and FDA adopted the National Commission’s recommendation.⁹⁹

* * *

Taken together, the three categories of research that can be approved by a local IRB constitute the majority of pediatric research approved and conducted in the United States. Where a protocol does not fall into one of these approvable categories, it is generally amended so that it conforms to local review requirements or else it is denied approval. Only rarely is such a protocol elevated for national-level review under section 407. (See Pediatric Research Requiring National-Level Review—Higher Risk and No Prospect of Direct Benefit, Chapter 2.) These regulatory provisions for local IRB review place strict, ethically sound limits on the degree of risk to which children can be exposed in research, and from the time they have been in place, they have permitted and indeed fostered research leading to interventions for the most common childhood illnesses and conditions.¹⁰⁰

Pediatric Research Requiring National-Level Review—Higher Risk and No Prospect of Direct Benefit to Healthy Participants (Section 407)

Although the National Commission created a mechanism for local approval of greater than minimal risk research with children affected by a disorder or condition, it did not develop a set of criteria for local IRBs to approve higher-risk research with healthy children or research where the risk is greater than a minor increase over minimal risk. This latter type of research was reserved for evaluation and approval by a national panel of experts and the Secretary of HHS, later codified as section 407. The National Commission struggled with the idea of involving children in such research with no prospect of direct benefit to the individual child participant, but recognized that there might be extraordinary circumstances in which the dangers to children as a class, or the community as a whole, that would result from excluding children from research would be so great that they might require society reluctantly to accept a higher level of research risk. For instance, in the event of a pending epidemic that could be stemmed by testing a novel vaccine with children, the circumstances might require this reluctant acceptance of levels of risk otherwise unacceptable in pediatric research (e.g., higher risks involved in determining dosing specifications for particular age groups).

Acknowledging that every such situation would involve different considerations that could not be precisely resolved in the abstract, the National Commission concluded that it would be preferable to debate the matter in an actual situation where the “real issues and the likely costs of any solution can be more clearly discerned.”¹⁰¹ In providing the opportunity for considered debate in light of more specific circumstances, the National Commission went a step further, calling for public input as well, stating that the moral obligation to protect the community (to the extent ethically and practically possible) and the prohibition against using unconsenting persons at considerable risk to their well-being for the promotion of the common good were of such import that debate on how to reconcile the obligation and prohibition must be held publicly.¹⁰² The National Commission recommended that research entailing this level of risk could only be approved as an “exception to the general rules” (i.e., when “[t]he outright prohibition of such research on grounds of risk might have consequences which themselves appear unethical”) and could only

go forward after (1) an IRB determines that for “urgent or unique” reasons the research should be permitted, and (2) the research is reviewed and approved at the national level to determine that it does not violate the principles of respect for persons, beneficence, and justice, with opportunity for public comment.¹⁰³ Additionally, appropriate parental permission and meaningful child assent would be required. The National Commission recommended that this national-level review include judgment by the Secretary of the responsible agency and that approved research should be delayed pending congressional notification and a reasonable opportunity for Congress to take action regarding the proposed research.¹⁰⁴

As enacted, the regulations provide that research may be approved if (1) *an IRB determines* that the research “presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children” but is not approvable under sections 404 to 406, and (2) upon convening a panel of experts and soliciting public comment, *the Secretary of HHS determines* that (i) the “research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;” (ii) “the research will be conducted in accordance with sound ethical principles;” and (iii) adequate provision is made for permission of parents and guardians and meaningful assent (or affirmative agreement) of children.¹⁰⁵ This structure creates three independent bodies that must review or approve any protocol submitted for assessment under section 407: (1) the local IRB, (2) the national panel of experts, and (3) the Secretary of HHS.

As evidenced by the language of section 407, HHS (and FDA in its regulations) modified the National Commission’s recommendation. The provision adopted by HHS (and FDA) does not provide for notification of Congress and sufficient delay for Congress to intervene. The reasons for this omission are unclear. In addition, the regulations depart from the National Commission’s recommendations by providing for an ad hoc panel of experts to conduct the national-level review, rather than a standing “[N]ational [E]thical [A]dvisory [B]ody.”¹⁰⁶ Unlike a standing committee, a system that HHS expected to prove “cumbersome, inflexible and unadaptable to the variety of different research problems likely to be encountered within the scope of the Department’s activities,” the agency hoped that an ad hoc structure would provide the flexibility

necessary to convene sufficiently expert individuals in a range of scientific specialties, ethics concentrations, legal fields, and other relevant disciplines for a given protocol.¹⁰⁷

Similarly, regulations adopting national-level review, rather than enumerating the principles in the National Commission's recommendation (respect for persons, beneficence, and justice), simply require that research be conducted in accordance with "sound ethical principles."¹⁰⁸ Although the provision permits necessary flexibility for review of research required by extraordinary circumstances, many expert panels have reported great uncertainty in determining whether a protocol was consistent with sound ethical principles, especially in the context of extraordinary circumstances that would justify approval.¹⁰⁹

NATIONAL-LEVEL REVIEW CASE STUDY: DRYVAX (SMALLPOX VACCINE) PROTOCOL

In 2002, an independent panel reviewed a protocol to test smallpox vaccine in 40 children, 2 to 5 years of age. Because smallpox was eradicated in 1979, no manufacturer still produced the vaccine and only a limited supply of stockpiled vaccine doses remained. Motivated by concerns about a possible bioterrorism attack using smallpox virus, the study was intended to demonstrate the safety of diluted vaccine (and its immune response), allowing emergency responders to stretch the existing supply.

Reviewers agreed that the existing evidence about adverse reactions and secondary infections in adults suggested that the vaccine trial would pose more than minimal risk to children. The experts struggled, however, with putting these risks in context. Because they could not foresee the likelihood of a bioterrorism attack, many found it difficult to quantify the possibility of future benefit to children as a class. Further complicating the reviewers' considerations was news of a potentially safer, next-generation vaccine in development, which might be available by the time a smallpox attack occurred. Reviewers also debated subject selection problems that might result if only parents particularly concerned about bioterrorism attacks permitted their children to participate.

Ultimately, HHS did not approve the protocol because biopreparedness plans changed, meaning that DryVax would not be used for children in an emergency.

Source: Quigley, R. (2004). Uncertain benefit: The public policy of approving smallpox vaccine research. *American Journal of Public Health*, 94(6), 943-946.

In practice and as permitted by regulation, national-level review is used primarily for research that could not otherwise be approved under another section in Subpart D (sections 404 to 406), but most of the research to date that has been considered under section 407 has not risen to the level of extraordinary circumstances. This practice is in tension with both the tenor of the National Commission’s discussion and the language of its recommendation. However, the ethical difficulties inherent in enrolling healthy children as experimental controls create persistent challenges difficult to resolve in a way that would permit approval under sections 404 through 406.¹¹⁰ Healthy controls are scientifically essential to ensure high quality scientific results. Such broad application of the national-level review process might result from inadequate specification of the term “serious” or from the codification of section 407 as a “catchall” provision. Nonetheless, while national-level review has been used more frequently in recent years, it remains rare. From 1991 to 2012, this level of review has been used in only 14 cases, 10 of which were approved.¹¹¹

Conclusion

The ethical foundations for research with children are rooted in long and widely held ethical principles—respect for persons, beneficence (and non-maleficence), justice, and democratic deliberation—articulated and embodied by the National Commission’s recommendations in 1977 and later codified in federal regulations. In general, the current ethical and regulatory framework functions well, fostering research and advancing medical progress for children while adequately protecting them. Although there are historical examples of unethical research with children, most of these predate the current regulations.

The Belmont principles, in conjunction with the principle of democratic deliberation, continue to guide contemporary pediatric research and set the backdrop for the Bioethics Commission’s deliberations on the ethics of MCM research with children. In the next chapter, the Bioethics Commission examines how the characteristics of MCM research and these ethical principles interact to present unique circumstances to consider when deciding whether to proceed with pediatric MCM research in general and with specific MCM protocols.

CHAPTER 3
Ethical Considerations for
Pediatric Medical Countermeasure Research

The Secretary of Health and Human Services (HHS) requested that the Bioethics Commission analyze the ethical issues associated with conducting medical countermeasure (MCM) research with children, including an analysis of both pre- and post-event studies of anthrax vaccine adsorbed (AVA). In this chapter, the Bioethics Commission, supported by the long-held principles enumerated in Chapter 2, concludes that society's duty to children requires a necessary, even if not sufficient, limit on the level of research risk to which children can be exposed for the benefit of others. This risk ceiling, above which only limited and previously outlined exceptional circumstances allow us to pass, governs even the unique circumstances of MCM research.

Ethical Grounding

Ethical biomedical research is motivated by principles set forth in the *Belmont Report* and embodied by the work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the National Commission)—respect for persons, beneficence (and its corollary non-maleficence), justice, and democratic deliberation. Additional considerations relating to children are outlined in the National Commission's report *Research Involving Children* and codified in 45 C.F.R. Part 46, Subpart D and 21 C.F.R. Part 50, Subpart D. (In this chapter, as in Chapter 2, the Bioethics Commission adopts shorthand, referring only to HHS regulations in the text, although the discussion encompasses the provisions of Subpart D as codified by both HHS and the U.S. Food and Drug Administration (FDA).)

Central to any analysis of pediatric research is the fact that children are ethically and legally unable to consent to assume research risks. Respect for persons in the context of pediatric research requires that researchers obtain both parental permission and meaningful child assent to participate. Although meaningful assent (or dissent) is distinct from consent, it nevertheless plays an important role in respecting children as persons. Young children differ from the oldest children in their moral development, which affects their ability to meaningfully assent (or dissent) to research participation. Children who have the ability to provide meaningful assent for participation in MCM research without the prospect of direct benefit, and who instead demonstrate meaningful dissent, are entitled to have their dissent respected, regardless of their parents' permission. The critical consideration is that assent and dissent

be meaningful. For example, a toddler, unable to provide meaningful assent, who expresses distaste for an injection is not expressing meaningful dissent.

In conjunction with respect for persons, beneficence obligates us to recognize additional duties owed to children as vulnerable persons. As outlined in Chapter 2 of this report, beneficence guides the risk-benefit assessment in research. Reducing research risk to children to the lowest possible level by considering all possible alternatives—one of five considerations offered in the *Belmont Report*—requires that researchers test interventions as extensively as possible with computer models, animals, or adults (individuals who can legally and ethically consent) in order to better understand and minimize research risks before testing interventions with children.¹¹² Beneficence also requires that we safeguard the health of children outside the research context, which can include providing evidence-based treatments and, in the case of public health preparedness, safe preventive and therapeutic interventions, including MCMs. Justice, which calls for equitable distribution of research burdens, in combination with respect for persons, beneficence, and non-maleficence, requires that adults take on greater risk so that children bear no more risk than necessary.

Together these principles support the ethical conclusion that research with children should generally pose no greater than minimal risk to participants unless it offers the prospect of direct benefit (45 C.F.R. § 46.405 (section 405)) or is likely to generate vitally important knowledge about the participants' condition (45 C.F.R. § 46.406 (section 406)). In the context of pre-event pediatric MCM research where neither exception applies, this means that all necessary prior testing should be done to identify, understand, and characterize the risks in order to conduct research that could be classified reasonably as minimal risk (approvable under 45 C.F.R. § 46.404 (section 404)); posing risks no greater than those of everyday life or a routine medical examination whenever possible.

If it is not possible to conduct an informative minimal risk pre-event pediatric MCM study, and the research poses no more than a minor increase over minimal risk, the proposed research may go forward only after national-level review, as set forth in 45 C.F.R. § 46.407 (section 407) and specified later in this chapter. Though section 407 allows for the potential approval of research

posing more than a minor increase over minimal risk in other circumstances, the Bioethics Commission determined that this greater level of research risk is ethically impermissible in the MCM context. Certain kinds of pediatric MCM research seem to meet the standards of “extraordinary circumstances” envisioned by the National Commission. Pediatric MCM research requires narrower risk limits than might be permitted in other exceptional types of pediatric research under section 407, however, because it is distinct from most other pediatric research in ethically relevant ways as highlighted in Chapter 1 of this report and further discussed below.¹¹³ Moreover, because children have no legally or ethically recognized capacity to consent to assume risks—and because they are vulnerable individuals who need to be protected from undue risks undertaken for the benefit of others—the Bioethics Commission considered this approach to pre-event MCM research with children to be fully consistent with established ethical principles.

In the context of post-event pediatric MCM research, research risks also must be minimized. Yet the ethical considerations differ from pre-event MCM research because pediatric research participants likely will have been exposed to an agent, meaning that research could yield vital information about their condition (section 406), and participants might have already received the MCM under investigation as a treatment measure, reducing research risks to minimal (section 404) or creating the potential for direct benefit to participants (section 405).¹¹⁴ When children receive an untested MCM, it is ethically imperative that researchers collect as much data as possible to inform and protect both those who have received it and other children who in the future might need such treatment in an emergency. Research protocols must be in place for rapid deployment, and groundwork for extensive and effective community engagement must be prepared. Also of paramount importance, exceptional care must be taken to ensure that research protections such as fully informed parental permission and meaningful child assent are observed to their fullest extent.

Although pediatric MCM research can be conducted either before a bioterrorism event occurs—as a pre-event study—or after a bioterrorism event occurs—as a post-event study, pre- and post-event studies present different ethical and logistical concerns. In pre-event research, no research participants have yet been exposed to the agent, meaning the research will not offer the

prospect of direct benefit to individual child participants or the prospect of valuable knowledge about the participants' condition. Participants in post-event research have either already been exposed to the agent or have a greater likelihood of being exposed in the near future and might have already received the MCM under investigation. Post-event research risks, therefore, are generally limited to those involved in the active or passive surveillance of participant reactions to the MCM. Because these types of research raise different ethical and logistical concerns, pre- and post-event studies are addressed separately and in turn. For the purposes of this report, those studies conducted when a threat is imminent (i.e., it is predictably coming quickly and there is little time for deliberation) are understood to pose ethical and practical concerns that track those of a post-event study even if technically conducted pre-event.¹¹⁵ These concerns will be addressed in greater detail below.¹¹⁶

Pre-event Studies

Pre-event pediatric MCM research will generally be conducted with healthy children and offer no prospect of direct benefit to participants. Further complicating its conduct, pre-event MCM research presents challenging ethical characteristics, involving (1) health conditions that might pose considerable danger to children as a class—but danger that could be mitigated by exposing a small group of healthy children to research risks; (2) health conditions that no child has yet contracted and that result from events that have an unknown and unknowable likelihood of occurrence; and (3) research that would produce results that we expect and hope never to use. Given these characteristics, pre-event research cannot be considered to offer the prospect of direct benefit to research participants, and therefore cannot be approved under section 405. Pre-event MCM research also cannot be approved under section 406 because the participants do not have a condition about which important generalizable knowledge can be obtained. All such pre-event pediatric MCM research therefore must either be approved under section 404, which requires that research risks be minimal, or—in exceptional circumstances, as set forth in greater detail below—under section 407.

To the extent that sufficient testing in adults or animals can demonstrate that the risks of pre-event pediatric MCM research could be considered minimal, studies should be reviewed and approved under section 404. If it should prove

impossible to conduct research that can be reasonably classified as minimal risk, then the level of allowable risk must be capped at a minor increase over minimal risk, and the pre-event pediatric MCM research proposal must undergo national-level review. National-level review under section 407 should be permitted only in rare circumstances or, as the National Commission put it, in “exceptional situations... in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk.”¹¹⁷

Pre-event Studies Posing No More Than Minimal Risk Approvable under Section 404

Whenever possible, informative pre-event pediatric MCM research should be designed in a way that children are only exposed to minimal risk. Such research would therefore be approvable under section 404.¹¹⁸ Designing MCM studies as minimal risk requires a thoughtful and carefully executed research plan. Since most bioterrorism events will affect both adults and children, thorough testing in adults, who can consent to assume risk on behalf of others, must be completed before conducting research with those who cannot consent. Prior testing can help identify, understand, and characterize the risks of research. Once these risks are properly understood, to the extent it is possible to design and conduct informative minimal risk research with the youngest adults (e.g., 18 years of age), it might be possible that the same research design—modified in accordance with information obtained from prior research—could form the basis of a study that would similarly be minimal risk with the oldest children (e.g., 16 and 17 years of age). Moreover, adolescents aged 16 and 17 could provide meaningful assent to participation which, along with parental permission, would allow the research to proceed. Once minimal risk research is conducted with the oldest children, research determined to be minimal risk by incorporating any new data from this prior research could be conducted with the next youngest group of children. To the extent that it is possible to infer minimal risk from research with the previous cohort, “age de-escalation,” a process typical of vaccine development trials, would continue as a stepwise series of minimal risk protocols through to the youngest group of children.¹¹⁹

It is important to recognize that inferring minimal risk does not depend solely on whether an intervention is determined to be “safe” in adults. Adverse event data, for example, will not definitively determine whether a study meets the regulatory “minimal risk” standard. In addition to the risk associated with the intervention itself (which is informed by safety information and adverse event data), reviewers and researchers must account for the risks associated with research procedures as well (e.g., blood draws, if part of the research design).

Moreover, the Bioethics Commission recognized that, as a general matter, studying a previously untested therapeutic with children is often categorically classified as more than a minor increase over minimal risk.¹²⁰ The age de-escalation process contemplated here, however, requires researchers to collect data and assess risk on the most similar group and infer the level of risk, when possible, to the next youngest age group. If minimal risk studies can be done with the youngest adults, for example, it might be possible to infer that a similar minimal risk study design can be done with the oldest adolescents.

Not treating all children (i.e., 0 to 17 years of age) as a single group or class enables careful and thoughtful inference. Because very young children differ physiologically from adults (and even older children) in significant ways, extrapolating adult data about risk to all children (0 to 17 years of age) is quite difficult and involves a high degree of uncertainty. While initially there might be a dearth of relevant pediatric data, under an age de-escalation approach, researchers and reviewers might be able to make an empirical finding that the research risk is no greater than minimal or a minor increase over minimal for the next lower age group. The Bioethics Commission concluded that cautious and scientifically sound age de-escalation, beginning with the youngest adults and progressing to the oldest children, can yield important data that will better inform the degree of risk posed by research.¹²¹ Although the data obtained through age de-escalation studies might show that the risks of research are still too high to justify its conduct, in other cases, the availability of more targeted and relevant data (and consideration of a more limited segment of the pediatric population) may permit extrapolation with greater certainty in judging the level of risk posed by a given protocol.

The specific design of age de-escalation trials will vary depending on the intervention being tested and its mechanism of action, as determined through

early clinical trials and thorough testing in adults. Age de-escalation need not and should not be based solely on a participant's age: additional developmental markers can and should be considered. While pediatric drug dosing is typically determined by a combination of age and body weight, maturational differences in absorption, metabolism, and elimination of drugs make use of age and weight alone less than ideal.¹²² Similarly, pediatric vaccine dosing is sometimes determined on the basis of body weight, route of administration, and maturation, but MCM research trials should take into account more granular physiological factors. Relevant demarcated steps for the process of age de-escalation should be clearly defined in the research plan and might be based on appropriate biological characteristics such as chronological age or stage of development (e.g., post-pubescent, pubescent, pre-pubescent, adolescent, school age, early childhood, toddlerhood, and infancy). For example, if the mode of action of the intervention might be affected by the metabolic, hormonal, immunological, and body composition changes that occur at predictable developmental stages of childhood, such as puberty, then age de-escalation should be carefully designed to account for these changes rather than solely accounting for age by chronological year.

A focus on informed age de-escalation protocols will help to minimize risk in most pre-event pediatric MCM research. There are, however, contextual limits to the employment of this strategy. Stepwise age de-escalation studies are time-intensive, particularly if the aggregated results of initial studies must be analyzed for use in designing the trial with the next lower age group and if each new trial requires individual IRB approval. In the event that the U.S. government receives credible intelligence on the development and planned deployment of a particular bioweapon, there might not be adequate time to complete sufficiently cautious age de-escalation protocols. The recommended use of age de-escalation assumes a situation in which there is no immediate threat of deployment.

Additionally, there are situations in which age de-escalation trials might not be appropriate based on the anticipated difference in impact that an agent could have on children compared with adults, or on the possibility that an agent might be used specifically to target children. Children, along with adults, would be affected in generalized bioterrorism attacks, but children could also be targeted specifically.¹²³ Certain biohazardous threat agents could have a

greater impact on children than on adults. A smallpox outbreak, for example, likely would affect children disproportionately due to the waning effects of herd immunity since the effective eradication of the disease and cessation of immunization in the United States in 1972. Children could also be targeted by location (e.g., schools) or through the mechanism of delivery, such as targeting the milk distribution system. Given that children between the ages of 2 and 11 years consume approximately twice as much milk as adults, an attack of this nature would pose a significant threat to children.¹²⁴ While many bioterrorism agents affect both adults and children, and thus MCMs should be tested in adults first, evidence exists that children could be intentionally targeted through both method of distribution and specific agents.¹²⁵

Although the potential targeting of children in a bioterrorism attack stresses the importance of conducting pediatric MCM research, such research, even when minimal risk, must be ethically sound. For example, ethical pre-event pediatric MCM research must assure a developmentally appropriate, meaningful assent process for potential child participants, administered in conjunction with the process employed to obtain parental permission.¹²⁶ Fully informed parental permission and meaningful child assent is especially important in the case of MCM research. A person independent of the study team should monitor consent or oversee the process of obtaining parental consent and meaningful child assent even in minimal risk studies. The consent monitor should be an independent entity, without conflict of commitment or conflict of interest in conducting the research.

Ethically sound pre-event pediatric research must also ensure that the costs of any resulting harm or injury do not fall on the injured research participants—even in minimal risk studies. This means that researchers must ensure that compensation for injuries arising from MCM research is accessible under the Public Readiness and Emergency Preparedness (PREP) Act or through an alternative mechanism. (See Compensation for Research-Related Injury, Chapter 3.)

Whenever possible, pre-event pediatric trials should employ age de-escalation strategies that provide additional protection to the most vulnerable members of the group (the youngest children) by beginning with those who are less vulnerable (young adults). If prior testing of young adults makes it reasonable to infer that such research would be of minimal risk to the oldest children,

conducting minimal risk research with those in their late teens would allow researchers to identify, characterize, and understand research risks before moving to younger, more vulnerable, groups of children. In the event that age de-escalation is impossible—due to, for example, an inability to extrapolate the rate of adverse events between adults or older children and younger children, or insufficient time available for testing—MCM research might need to be considered under section 407, provided it is no more than a minor increase over minimal risk. (See Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407, Chapter 3.) In all cases, ethical safeguards such as fully informed parental permission, meaningful child assent, and treatment or compensation for research-related injuries must be provided.

Recommendation 1: Pre-event Pediatric Medical Countermeasure Research Risk Limited to Minimal Except under Extraordinary Circumstances

Pre-event pediatric medical countermeasure testing should be conducted with a research design posing only a minimal level of research risk except under extraordinary circumstances. If pre-event pediatric medical countermeasure research cannot be conducted as a minimal risk study, research that exposes children to no more than a minor increase over minimal risk—a level that is still very limited and poses no substantial risk to health or well-being—should proceed to a national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug regulations at 21 C.F.R. § 50.54.

Recommendation 2: Risk in Pre-event Pediatric Medical Countermeasure Research

Before beginning pre-event medical countermeasure studies with children, ethically sound modeling, testing with animals, and testing with the youngest adults must be completed to identify, understand, and characterize research risks. If pediatric research is determined to be minimal risk and is to be conducted, progressive age de-escalation should be employed whenever possible from the oldest age group of children to the youngest group necessary to provide additional protection to the youngest and most vulnerable children, and to ensure that data from an older age group can inform the research design and the estimate of risk level for the next younger age group.

Application to Trials of AVA with Children: Minimal Risk Pre-event Trials of AVA with Children

An AVA trial with children that is approvable under section 404 must present no more than minimal risk to participants. Provided that all necessary prior testing of AVA has been conducted in adults, and in the event that it is possible to conduct an informative minimal risk pre-event trial with the youngest adults (i.e., 18 years of age), it might be possible to design and conduct minimal risk pre-event research with the oldest cohort of children (i.e., 16 and 17 years of age). Moving from AVA trials in the youngest adults to the oldest cohort of children only can proceed under section 404 if the research is minimal risk in young adults, and the data collected are sufficient to conclude that such research could be considered minimal risk in the oldest cohort of children.

Available Data

The safety, immunogenicity (the capability of a vaccine to stimulate a specific immune response), and dosing of AVA have been evaluated in both animal studies and adult human studies. Based on available data, AVA is approved by FDA “for the active immunization for the prevention of disease caused by *Bacillus anthracis*, in persons 18 through 65 years of age whose occupation or other activities place them at high risk of exposure.”¹²⁷ AVA has been distributed widely to adults—as of 2001, approximately 2.1 million doses of AVA had been distributed to members of the military.¹²⁸

AVA safety has been evaluated in adults through both active and passive surveillance studies, and its safety is comparable to other vaccines regularly administered during routine medical appointments.¹²⁹ Data in adults indicate that the mild and moderate adverse events associated with AVA are no worse than for other vaccines.¹³⁰ Although vaccination with AVA results in a higher incidence of mild allergic reactions than some other more routine vaccines AVA is less allergenic than vaccines that are produced with eggs (e.g., yellow fever vaccine).¹³¹ Among mild reactions, tenderness (about 1 person out of 2) and redness (about 1 out of 7 men and 1 out of 3 women) near the injection site are most common.¹³² Less common are mild reactions such as itching (about 1 out of 50 men and 1 out of 20 women), development of a lump (about 1 out of 60 men and 1 out of 16 women), or bruising (about 1 out of

25 men and 1 out of 22 women) at the injection site. Systemic events—such as fever, malaise, and myalgia—although associated with receipt of AVA, are much less common than injection site reactions, and are similar in both rate and type to events observed following receipt of other vaccines that are routinely administered.¹³³ Accordingly, it might be possible to conclude that the administration of AVA in adults is minimal risk because “the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered ... during the performance of routine physical ... examinations or tests.”¹³⁴

AVA’s immunogenicity has also been evaluated in adults, but the immune response it elicits is not as well characterized as its safety. While the mechanism of immunogenicity is understood and has been qualitatively observed, the quantitative relationship, or the precise level of antibody that confers protection against anthrax, is not known.¹³⁵

Data regarding the efficacy of AVA come from vaccine trials in animals whose immune responses are similar to adults, including rhesus monkeys and, to a lesser extent, rabbits.¹³⁶ These studies have shown that AVA is most effective against anthrax when combined with antibiotics and given before the onset of clinical illness.¹³⁷ Antibiotics treat the immediate infection while the vaccine provides protection against future infection from the dormant spores that remain after the course of antibiotics has been completed. Information regarding the efficacy of AVA in adults also comes from one human study, a 1962 experiment in which mill workers at risk of cutaneous anthrax exposure were given an early anthrax vaccine (not AVA).¹³⁸ The usefulness of this adult data is limited because the research addressed cutaneous anthrax rather than inhalational anthrax, and the vaccine tested was only a precursor to AVA. Observational data in humans also provide evidence of efficacy in adults.¹³⁹

Application of Available Data

In vaccine development, whenever possible, trials are first conducted with adults. Pediatric trials begin only after adult safety, immunogenicity, and efficacy (when possible) are determined, and are often conducted using age de-escalation.¹⁴⁰ The rationale and design of age de-escalation depends on the nature of the disease, the target population for the vaccine, and what is known about immune response in children. In the context of preventive HIV

vaccines, a circumstance in which vaccines would ultimately be marketed for both adults and children, FDA has stated that the amount and kind of adult data that are needed to support initiation of pediatric studies depends upon: (i) “the strength of the adult safety and immunogenicity data generated,” (ii) “what is known about the investigational vaccine in terms of its relationship to well characterized vaccines or novel vectors or production methods,” and (iii) “the relationship of documented immune response to protection.”¹⁴¹

Various types of information must still be gathered before pediatric AVA trials can proceed. Before moving from adult AVA trials to pediatric trials, data characterizing adverse reactions of AVA for persons 18 years of age are required. Researchers should begin with a thorough examination of adverse event data in the youngest adult AVA recipients before they can infer that an AVA trial with the oldest children (e.g., adolescents ages 16 and 17) poses a minimal level of risk. Additional dosing studies in the youngest group of adults must also be completed. Specifically, studies evaluating the adequacy of different dosing strategies in adults are required before pediatric studies may be conducted.¹⁴² Trials with children should begin only after all adult data required by FDA to scientifically and ethically justify pediatric research are acquired. The U.S. Centers for Disease Control and Prevention (CDC) and the Institute of Medicine also have recommended additional investigation into long-term side effects, alternative dosing methods, and quantitative determination of correlates of immunity in animal models.¹⁴³

Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407

There will be instances in which it will be impossible to design minimal risk pre-event MCM research. In such cases, national-level review under section 407 would be required, but should proceed only if researchers can demonstrate that the research poses no more than a minor increase over minimal risk to participants.

A minor increase over minimal risk is only a narrow expansion of minimal risk; research at this risk level should not pose any significant threats to a child’s health or well-being.¹⁴⁴ This risk standard is codified in section 406 (which governs research with no prospect of direct benefit but that is likely to yield generalizable knowledge about the participants’ condition) and, given

the unique characteristics of pre-event pediatric MCM research discussed above and the fact that children cannot consent to participation, the Bioethics Commission concluded that this risk standard also should apply and set the upper limit to greater than minimal risk pre-event MCM research approvable under section 407.¹⁴⁵ Pre-event MCM research offers no prospect of direct benefit to pediatric participants. Moreover, it is uncertain that anyone, let alone any children, will ever benefit from such research because the risk of a bioterrorism event that would require the use of any given pediatric MCM is thus far no more than speculative. While the Bioethics Commission did not rule out the possibility that other sorts of extraordinary circumstances might warrant exposing children to slightly more than a minor increase over minimal risk in research from which they do not have any reasonable expectations of benefit, the inherent uncertainty of an exposure that would affect children in the future strongly favors capping the permissible risk in pre-event MCM research at no more than a minor increase over minimal. Further, investigators should explore all possible strategies for conducting such research in a manner that would involve no more than minimal risk.

A minimal risk research design for pre-event pediatric MCM research might be impossible, however, for a variety of reasons. Chief among the potential barriers is that inferring risk between groups of children in different developmental stages during the age de-escalation process might prove impossible. (See Pre-event Studies Posing No More Than Minimal Risk Approvable under Section 404, Chapter 3.) For example, it might be impossible to infer that an intervention considered to be minimal risk with pubescent children will similarly pose only minimal risk when tested with pre-pubescent children. Alternatively, researchers might find that, even with comprehensive adult testing, potential research risks should not be considered minimal for pediatric participants due, for example, to the risks inherent in any use of the tested product. Other obstacles might arise if the potential MCM is designed to counter an agent that specifically targets some aspect of pediatric physiology (making prior testing with adults unethical or uninformative), or if there is no time to conduct full age de-escalation.

Recommendation 3: Pre-conditions to National-Level Review of Pre-event Pediatric Medical Countermeasure Research

Pre-event pediatric medical countermeasure research may proceed to national-level review under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54 only when researchers have demonstrated and reviewers concur that a minimal risk study is impossible and the proposed study poses no more than a minor increase over minimal risk to research participants. In part because of the inherent uncertainty of a bioterrorism attack, pre-event pediatric medical countermeasure research posing greater than a minor increase over minimal risk should not be approved under 45 C.F.R. § 46.407 or 21 C.F.R. § 50.54.

When research meets these two threshold conditions—minimal risk research is impossible and the proposed research presents no more than a minor increase over minimal risk—the framework specified below provides the considerations necessary to approve a pediatric MCM research protocol under section 407. While this framework might provide useful guidance for other types of 407 review, the Bioethics Commission developed it specifically for pre-event pediatric MCM research. The term “407 review” here refers to review under both HHS provision 45 C.F.R. § 46.407 and FDA regulation 21 C.F.R. § 50.54.

Specifying a Framework

Under section 407, the Secretary of HHS, in consultation with an independent panel of experts, can review and approve pediatric research, including investigations with healthy children that involve greater than minimal risk and offer no prospect of direct benefit to participants.¹⁴⁶ Before approving this type of research, however, by regulation, the Secretary must determine that the protocol under review meets *all* of the following conditions required under section 407:

1. The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;
2. The research will be conducted in accordance with sound ethical principles; and

3. Adequate provisions are made for soliciting the permission of parents or guardians and the meaningful assent of children.¹⁴⁷

The Bioethics Commission’s recommended framework, structured around the three conditions for national-level review, clarifies the circumstances in which proposed research presents a “reasonable opportunity” to address a “serious problem,” specifies a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with “sound ethical principles,” and reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent. Decision makers should assess proposed pre-event pediatric MCM research that poses more than minimal risk using this framework in order to ensure that all the necessary aspects of a study have been evaluated and found ethically permissible before moving forward.

Importantly, only after the Secretary of HHS, with the advice of an independent panel, has found it ethically permissible to proceed would parents be asked to decide whether to enroll their children in research.

1. Does the Research Present a Reasonable Opportunity to Further the Understanding, Prevention, or Alleviation of a Serious Problem that Could Affect the Health or Welfare of Children?

In order to satisfy the first condition for approval under 407 review, proposed research must present “a *reasonable opportunity* to further the understanding, prevention, or alleviation of a *serious problem* affecting the health or welfare of children.”¹⁴⁸ To provide more granular guidance, the Bioethics Commission specified the type of problem that qualifies as a sufficiently “serious problem” and reiterated the importance of identifying a “reasonable opportunity.”

A. Serious Problem

At the outset of 407 review for pre-event pediatric MCM research that poses more than minimal risk, decision makers must confirm that the proposed research addresses “a serious problem affecting the health or welfare of children.”¹⁴⁹ Evaluation of the seriousness of the problem is the first step of a 407 review because if there is no serious problem or threat of a serious problem to address, then enrolling healthy children in greater than minimal risk research is clearly unwarranted. This evaluation is conducted independently of

the merits of any particular protocol. As a matter of beneficence and respect for persons, it would be unethical to expose child research participants who cannot consent to unnecessary research risks or to any risk if a problem is not sufficiently serious. And, when a problem is serious, beneficence calls for investments (e.g., through research) to protect children from potential threats.

In the context of MCMs, a serious problem can be specified along at least two dimensions: (1) the consequences of exposure and (2) the likelihood of exposure. The panel reviewing a protocol must determine and advise the Secretary whether proposed research satisfies both of these criteria.

i. Seriousness Due to Consequences of Exposure

To determine the seriousness of the consequences of exposure, one must consider not only the magnitude of harm should an exposure occur, but also the vulnerability of children to exposure and the relative adequacy of any available therapeutic options or research alternatives.¹⁵⁰ In this assessment, reviewers should consider the anticipated public health and security responses at the federal, state, and local levels and their ability to mitigate the consequences of any exposure, as well as the existence and availability of other suitable alternative MCMs. Reviewers should also consider the possibility and sufficiency of post-event pediatric research to mitigate both the short- and long-term consequences of exposure.

Taking all of these factors into account, a serious problem is one in which the consequences of exposure are life threatening, permanently disabling, debilitating, or similarly grave. It is not enough that consequences are simply detrimental to the well-being of children; the detriment must be a crucial obstacle to the growth and development of children in order to support the conduct of research offering no prospect of direct benefit that poses a minor increase over minimal risk. Beneficence requires that, if the consequences are serious enough, we take measures to ameliorate the welfare of children as a class, including those who participate in research and future generations of children.

ii. Seriousness Due to Likelihood (or Threat) of Exposure

A second dimension of the seriousness of a problem is the likelihood of exposure. This dimension adds compelling urgency to the governmental obligation to take steps to reduce or prevent future harms to the public welfare,

and to the welfare of children more specifically. Fear of exposure, however, is not an appropriate measure of its likelihood.

Calculating the precise probability of an attack is impossible (unless an attack is known to be imminent, in which case the circumstances are essentially similar to those of post-event rather than pre-event research).¹⁵¹ Rather, in the face of inevitable uncertainty, those considering the potential for harm to children as a class should use the best quantitative and qualitative evidence available to inform firmly grounded beliefs that estimate the likelihood of future events. This analysis should take into account determinations of the threat based on established methods for assessing risk, such as the U.S. Department of Homeland Security Material Threat Determination or other assessments that inform it. Assessments should also incorporate, to the extent possible, considerations of imminence, the physical properties of the agent, the plausibility of accessing and producing a chemical or biological agent, the ease with which the agent could be deployed, or the possibility that a change in formulation or virulence might affect the severity and incidence of exposure.¹⁵² Evidence that an attack is relatively likely, as opposed to remote, supports the idea that the proposed research addresses a sufficiently serious problem.

The Bioethics Commission concluded that, as part of 407 review, the Secretary should provide reasons that the likelihood of exposure renders the problem a serious one. The Secretary's rationale should be made publicly known, even if the determination is based on classified information. For example, the Secretary could make an unclassified rationale publicly available or provide a classified rationale to authorized representatives of the public (e.g., members of Congress). Articulating an explicit rationale helps to ensure a rigorous deliberative process and holds decision makers accountable to the public. Accountability is particularly important in cases where the threat level is classified because this information is often held by small groups of people with specific credentials and role-related priorities.

EXAMPLES OF CIRCUMSTANCES THAT MIGHT PRESENT A SERIOUS PROBLEM

Concrete examples can inform what constitutes a “serious problem.” Current regulations were developed in the wake of polio outbreaks, and the National Commission pointed to examples such as an impending epidemic in which considerable dangers to children or to the community at large might be avoided or prevented by enrolling children in greater than minimal risk research. Additional hypothetical examples might include:

1. Large quantities of weaponized sarin gas have gone missing under suspicious circumstances. Sarin is estimated to be five hundred times more toxic than cyanide, and even non-lethal exposure is likely to have unknown long-term effects on a child’s neurological development. A new MCM offers a promising potential intervention, but has not yet been tested with children.
2. Smallpox, a disease that no longer occurs naturally, is stolen from a research facility. The possibility of exposure poses a threat to the community at large due to its infectiousness and high mortality rate; pediatric populations are especially vulnerable. Historically, physicians have only been able to treat the symptoms rather than combat the virus itself. Scientists have found one new antiviral agent that is effective in combating the disease. This new treatment has just been approved for use by adults.
3. Security sources reveal that while certain terrorist cells in unknown locations cannot currently deliver a “dirty” bomb—which would entail significant radiological exposure—they have both the intent and will to develop delivery capability within five years. A new form of therapy has been developed, and it has been tested and found safe in adults and older children. No testing on young children has yet been undertaken.

iii. Seriousness Due to “Vital Importance”

The Bioethics Commission drew insight in specifying what constitutes a serious problem from sections 404 through 406 and, in so doing, adopted language from section 406—a section that also regulates research offering no prospect of direct benefit to participants and involving more than minimal risk. Section 406 allows for research to be approved if the research is likely to generate knowledge of “vital importance for the understanding or amelioration of the subjects’ disorder or condition.”¹⁵³ Although in section 406 the knowledge sought can relate to any condition of a research participant, section 407 limits research to only that which is likely to yield knowledge about a serious problem. In specifying what constitutes a serious problem,

the Bioethics Commission recognized that the ethical standard for the information to be gained from a protocol approved under section 407 must also, at the very least, be as rigorous as the ethical standard established in section 406, and therefore the information to be gained must be of *vital importance* to addressing that serious problem as well.

“[T]he criterion for judging the potential contribution of research must, ethically, be as stringent for reviews conducted under Section 407 as for those conducted under Section 406.”

IOM. (2004). *Ethical Conduct of Research Involving Children*. Washington, DC: The National Academies Press, p. 134.

B. Reasonable Opportunity

In addition to being of vital importance to addressing a serious problem, the proposed MCM research must present a “reasonable opportunity” to further the understanding, prevention, or alleviation of that serious problem.¹⁵⁴ Although various natural and manufactured threats can present a serious problem, the gravity of the problem alone is not enough to justify the research if the research itself does not present a reasonable opportunity to learn something significant to developing or deploying an MCM.

To constitute a reasonable opportunity, the proposed protocol must be based on the current state of the science and must present an opportunity to learn about a specific MCM candidate that might be useful in protecting or treating children exposed to a serious threat. Research that can be expected to yield knowledge that improves the safety, availability, or feasibility of MCM delivery could meet this requirement. If research does not constitute a logical step toward ameliorating a serious problem, principles of ethical research—including beneficence and respect for persons—require that additional risks not be imposed on others, particularly those who cannot consent.

2. Will the Research be Conducted in Accordance with Sound Ethical Principles?

Drawing on the principles of respect for persons, beneficence, justice, and democratic deliberation, the Bioethics Commission proposed a rigorous set of ethical conditions that must be employed when assessing whether pre-event pediatric MCM research reviewed under section 407 will be conducted in

accordance with “sound ethical principles.”¹⁵⁵ These conditions fall into five general categories: 1) ethical threshold of acceptable risk and adequate protection from harm; 2) ethical research design; 3) post-trial requirements to ensure ethical treatment of children and their families; 4) community engagement in pre-event research; and 5) transparency and accountability.

A. Ethical Threshold of Acceptable Risk and Adequate Protection from Harm

Because children themselves cannot legally or ethically consent to research and its attendant risks, the level of research risk to which children can be exposed when there is no prospect of direct benefit is strictly limited—typically to the level of “minimal risk.”¹⁵⁶ Thus, consistent with the principles of beneficence and respect for persons, the level of risk to which the government—and researchers—can ask parents to expose their children is limited and small. Although parents may reasonably permit their children to engage in certain higher-risk activities (e.g., contact sports), the government lacks comparable latitude. When children are at serious threat of future exposure, however, there might be reason to reluctantly accept testing with a small amount more risk if minimal risk research is impossible. As argued above, pre-event pediatric MCM research risk should always be limited to no greater than a minor increase over minimal risk.

“[T]he question is to what extent we, as a society, think it’s appropriate to put that decision in front of a parent... .”

Nelson, S., Senior Pediatric Ethicist and Lead Medical Officer, Office of Pediatric Therapeutics, Office of the Commissioner, FDA. (2012). Presentation to the Presidential Commission for the Study of Bioethical Issues, May 17. Retrieved from <http://bioethics.gov/cms/node/708>.

Although the level of risk permitted under section 407 is not specified or limited by regulation, the distinct characteristics of pre-event pediatric MCM research warrant strict risk limits. In particular, because this research offers no prospect of direct benefit and the likelihood of an exposure in which the research results would be required is unknown and unknowable, children involved in pre-event MCM research must be protected by keeping research risks both limited and small.

It is generally accepted that children should be protected from harm, and, in the context of pediatric research, limiting the research risk to which children may be exposed is one means of ensuring such protection. Under the current regulatory

framework, research protections can be summarized as adequately protecting children from harm in light of the expected results of the research—that is, whether the research is of possible direct benefit to individual participants, of potential benefit to an identifiable class of children with a disorder or condition, or of potential benefit to all children as a class.

In the case of pre-event pediatric MCM research, there is no prospect of direct benefit to individual participants or benefit to an identifiable class of children because the likelihood of an attack is speculative. Rarely does a bioterrorism agent exist naturally in a weaponized form or in the quantity or virulence necessary to cause the breadth of harm expected during an attack. Given the particularly remote possibility that results of pre-event pediatric MCM research will be put to use—more so than in other types of research approved under section 407—and the legal and ethical incapacity of children to consent, when it is impossible to design a minimal risk pre-event pediatric MCM research trial, the only ethically tolerable level of risk is a minor increase over minimal risk.

This “minor increase over minimal risk” threshold has been described by the National Commission as a narrow expansion over minimal risk, entailing “no significant threat to the child’s health or well-being.”¹⁵⁷ Assessment of research risk should take into account the probability, magnitude, duration, and reversibility of harm.¹⁵⁸ Risks include both potential harms from the intervention itself as well as those that might occur as a result of the procedures associated with the research. Reviewers should also take into account commonly used assessments of what constitutes minimal risk or a minor increase over minimal risk in making their determination. The level of permissible risk to which children may be exposed under specified circumstances includes, for example, risks of conditions such as redness or moderate soreness at the injection site (both minimal risk), or missing a few days of school due to temporary low fever or malaise (minor increase over minimal risk), or procedures such as drawing blood (minimal risk) or a skin biopsy or chest X-ray (minor increase over minimal risk). Procedures that entail a significant likelihood of greater risks than these (such as lumbar puncture or bronchoscopy) are not acceptable within the context of pre-event pediatric MCM research.

Risk assessment is necessarily based on empirical data, but risks cannot be measured directly. Judgments about risk may be based on adult human data, animal studies, or pediatric use of the product for different indications. If there are insufficient data from these sources to support the conclusion that the intervention poses no more than a minor increase over minimal risk to child research participants, more data should be obtained. Where the data are inconclusive or no additional data can be obtained, the remaining conclusion must be that the risk is more than a minor increase over minimal, and the research should not go forward. The assessment must be based on data in each case, and although empirical certainty in such matters is impossible, decision makers must strive to make the best judgment possible based on the available data.

B. Ethical Research Design

Pre-event pediatric MCM research should be designed and conducted under conditions of the greatest scientific and ethical rigor. Determining whether research is ethical includes evaluating the scientific necessity of the proposed trials, the design of the research plan, the adequacy of available data from prior testing conducted in adults, the benefit of the proposed study over alternatives, and the fairness of subject selection.

i. Scientific Necessity

Research with children is a matter of scientific necessity if the important research question cannot be answered without an ethically permissible study involving children. Pre-event pediatric MCM research reviewed under section 407 should be conducted only if it poses no more than a minor increase over minimal risk and it is necessary to include children in order to learn how to protect children as a subgroup during a bioterrorism attack.¹⁵⁹ As a matter of respect for persons, safeguards must be provided to ensure that children, as members of a vulnerable population, are not exploited through participation in unnecessary research, the results of which could be obtained by other means. This determination should be made using a careful, systematic evaluation of all information, including possible alternatives.¹⁶⁰

ii. Research Plan

To be ethical, human subjects research in general—including pediatric MCM research—should be both scientifically valuable and valid, and conducted in accordance with an ethical research plan. The research plan is a broad, high-level overview of the research, which can encompass multiple studies that collectively inform the overarching research question. In the context of pediatric MCM research assessed under section 407, an ethical research plan and each experiment contained therein must be scientifically valid, minimize risks to child research participants by, for example, conducting small trials using age de-escalation, implement appropriate monitoring, and properly plan for later research—all while maintaining a level of risk that is no more than a minor increase over minimal. Taken together, these considerations contribute to upholding and honoring the principles of beneficence and respect for persons by minimizing and managing foreseeable risks to research participants, quickly identifying and ameliorating the consequences of unforeseen risks, and maximizing the potential benefits by incorporating plans to acquire additional data.

Scientific Validity. Scientific validity is required for ethical human subjects research. In pediatric MCM research, each study should be well designed to answer a specific question of importance to the protection of children; studies should be adequately powered, rigorous in data collection, and feasible.¹⁶¹ The research plan should be peer-reviewed and approved as scientifically valid before moving forward with participant recruitment.

Small Trials and Age De-escalation. An ethical research plan ought to minimize the number of children exposed to research risks while maintaining a large enough group to satisfy the requirements of scientific validity. Testing an appropriate MCM dosage in pediatric populations should take place only after adult trials have been completed to determine dosing, safety, and—for vaccines—immunogenicity. Following adult trials, an ethical research plan will usually start with a very small pediatric trial with the fewest number of children necessary in the oldest age group (typically 10 to 20 participants) to evaluate the safety of the most promising dose and route of administration, based on adult information before expanding to later-stage studies that might involve many more participants.¹⁶² Larger-scale trials conducted to identify

rare adverse events from MCM interventions would not be ethically justified in a pre-event setting. However, adverse event data must be collected in a post-event study, closely monitoring any adverse events after an MCM is deployed. (See Post-event Studies, Chapter 3.)

When appropriate, ethical MCM research with pediatric populations should also incorporate age de-escalation, a process by which MCMs that have been deemed safe in adults are tested first with older pediatric populations, followed by successively younger children in multiple steps, based on development-specific characteristics, as the risks are classified and minimized.¹⁶³ When age de-escalation is used, trials with each new age range are informed by the results of the earlier trials so that trends observed in dosage (e.g., per body weight) or adverse events in each age group are used to determine how to alter the experimental design to maximize safety for the next group of participants. Inferring risks from young adults to older children is discussed in greater detail above. (See Pre-event Studies Posing No More Than Minimal Risk Approvable under Section 404, Chapter 3.)

Appropriate Monitoring. Minimizing risks to participants—as required by beneficence, non-maleficence, and respect for persons—can be accomplished, in part, through appropriate monitoring. The safety of participants in certain studies should be monitored through a data safety monitoring board, an independent group of experts tasked with monitoring study data and participant safety while the research is underway. In addition, the use of a medical monitor—a pediatrician (or team of pediatricians) independent of the research team who monitors trial participants—should be included in the study design to monitor participants. Monitoring should include extensive patient follow-up, particularly when experimental interventions could carry lasting effects that might otherwise escape detection. Because pediatric MCM research reviewed under section 407 exposes children who cannot consent to a minor increase over minimal risk, rigorous safety monitoring—with a medical monitor and a data safety monitoring board—is necessary.

Proper Planning for Post-event Research. In the context of research responsive to the threat of a bioterrorism attack, ethical research planning must also include appropriate plans for post-event testing, either through a post-event research arm (when pre-event testing is ethically appropriate) or through a

separate post-event study proposal. To plan adequately for post-event research, pre-event approval and plans for post-event access to funding and expertise should be in place. (See Post-event Studies, Chapter 3.)

iii. Prior Adult Testing to Minimize Risk to Children

To minimize risks to potential research participants in pre-event pediatric MCM research, any proposed intervention should, to the extent possible, be thoroughly tested and found acceptably safe in adults with regard to the same issues that would be studied with children. Information learned from prior testing with adults—along with information from computer models, animal models, and prior comparable MCMs—can help identify proper dosing for initial testing in pediatric populations and characterize the risk level such research might impose. The condition of prior testing with adults is a matter both of non-maleficence—that is, not imposing unnecessary risks on more vulnerable individuals—and of respect for persons—which calls upon testing those who can consent before turning to more vulnerable populations who cannot. This condition applies to the extent that research with adults can be conducted ethically. Prior testing of an intervention with adult populations might not be possible or ethical if, for example, the intervention is only clinically indicated for children, is expected to cause serious adverse events in adults but not in children, or is otherwise not appropriate for use in adults.¹⁶⁴ Requiring that any proposed intervention be tested in advance with adults when appropriate helps to ensure that child research participants who enter into adulthood before the tested MCM is needed will have access to an adult formulation of the intervention if ever necessary.

iv. Sufficient Benefit over Alternatives

In the context of 407 review, a proposed pediatric MCM study must be expected to generate knowledge that would confer a sufficiently greater overall benefit to children as a class than would the most beneficial alternative, if any, that does not impose greater than minimal risk without the prospect of direct benefit.¹⁶⁵ Assessing comparators is required as a matter of beneficence, which dictates that we strive to minimize risks while maximizing benefits in the present and the future. Pre-event MCM research assessed under section 407 is only justified by beneficence if it imposes less risk of harming participants

than alternatives, including risks of other pre- and post-event research or current preparedness contingency plans for children.

Determining an appropriate comparator requires assessing various scenarios, such as the use of alternative existing therapies that have already been tested with children; administration of therapies that have not been tested with children, but are approved for use by adults; or even the prospect of a next-generation intervention not yet approved or in advanced development, but likely to be authorized at the time such an intervention might be necessary.¹⁶⁶

v. Fair Subject Selection

Fair subject selection is a necessary condition of ethical research, and is a particularly important safeguard in the context of pediatric research because all children are vulnerable. The principles of beneficence and justice require that the selection of research participants is fair, minimizes risks to and enhances benefits for individual participants, and fairly distributes research risks and benefits more broadly.¹⁶⁷ Rather than selecting subjects on the basis of vulnerability, privilege, or convenience, fair subject selection requires that a study's particular research goals be the primary basis for determining who should be enrolled in research.¹⁶⁸

In considering potential pediatric research participants for pre-event MCM research, the question becomes which members of this vulnerable class should be selected for inclusion. Certain standards provide guidance. For example, we should not include children who are burdened with multi-faceted vulnerabilities, such as those who are “institutionalized, cognitively or physically disabled, or wards of the state.”¹⁶⁹

Children enrolled as research participants should be at least as likely to benefit from the results of the proposed study as children who are not participating in research. Determining appropriate populations to accord with this standard is context dependent and should include considerations such as geography, parents' occupation, or other risk factors. Certain populations—for example, children living in urban centers—might be at greater risk of future exposure because they live near targets of bioterrorism and therefore might be more likely to benefit from the results of pediatric MCM research in the event of an exposure. In selecting sites for clinical trials, researchers should consider

locations in which participants are likely to be at elevated risk of exposure to the agent under investigation. Selection of particular sites could increase the chances that research participants would be among those likely to benefit from an intervention should an attack occur.¹⁷⁰ Other populations—including first responders who advocate that their families be among the first to receive MCMs in an emergency—might have a greater potential to benefit from pediatric MCM research as well.¹⁷¹

Additionally, in research that is particularly complex, and in which children are expected to take on more than minimal risk for no prospect of direct benefit, researchers should seek to enroll research participants who are best equipped to understand the consequences of participation. Enrolling children of parents who are particularly well informed about the purpose and limits of pediatric MCM research, for example, could mitigate some of the heightened concerns about such research. This might include children of MCM researchers, policy makers, and subject matter experts.

Some have also suggested that another group—families of military personnel—might be particularly well informed in situations where military personnel have already received the MCM being studied.¹⁷² Other factors, however, caution against selective enrollment of children of military personnel in pediatric MCM research. Military personnel work in environments with clear chains of command, and so might interpret encouragement to enroll their children in research as a tacit manifestation of duty. Military parents, their children, or both, might feel inappropriate pressure to participate given the hierarchical social structures that they inhabit. Further, while service members have volunteered to be exposed to higher risks than most civilians, their children have not. This is not to say that children of military personnel should be ineligible to enroll in pediatric MCM studies, just that they should not be singled out for participation, and it should be clear that there are no positive or negative repercussions in deciding whether to enroll one's child.

C. Post-trial Requirements to Ensure Ethical Treatment of Children and Their Families

Justice, which requires that the benefits and burdens of research be equitably distributed, gives rise to certain post-trial obligations to ensure that participants in pre-event pediatric MCM research reviewed under section 407 are

not disproportionately burdened as a result of their participation in research. First, there should be an adequate plan in place to equitably distribute interventions shown to be successful through research to all exposed children in the event they are needed. Second, compensation and care should be guaranteed for any child who incurs a research-related injury during participation in a pediatric MCM trial.

i. Distribution Protocol for All Children Tested or Assured

Pre-event pediatric MCM research is conducted to ensure that, in the event of an attack, children have access to the benefit and protection of tested MCMs at appropriate dosages. Accordingly, children who participate in pediatric MCM research assume the risks of research that promises no prospect of direct benefit, but that might benefit all children as a class in the future. Given its ethical grounding in the potential for future benefit, pediatric MCM research cannot be justified unless the presumed benefit to children as a class is assured—that is, a documented plan must be in place for the wide and equitable distribution of the intervention (should research support its use) to children that need it in the event of an attack.¹⁷³ Moreover, in order to respect those who agree to participate in pediatric research and to create a just distribution of benefits and burdens, those who participate must have access to the potential benefits of that research when appropriate. The assurance of an equitable and just distribution protocol guarantees delivery of the intervention to children in need, including any that participated in pre-event research.

In developing a plan that equitably and adequately accounts for the interests of research participants and future children, researchers and government officials should use successful extant distribution plans for existing MCMs as models to distribute the experimental intervention in the event of an emergency. To the extent possible, this plan should be proven and should include provision for adequate quantities of MCMs.¹⁷⁴

Children who participate in research also should not be disadvantaged by such participation beyond the imposition of research risks. To the extent possible, the research protocol should ensure that research participants are not disadvantaged in an emergency situation as a result of their participation in pediatric MCM research. For instance, participation in a pediatric MCM trial for an experimental vaccine should not preclude a child from receiving the

eventual approved vaccine in the event of an attack, even if the vaccine supply is low, due to the assumption that the child might have residual immunity from their participation in the earlier research. Research participants should have the same access to the vaccine as other children who have been exposed to an agent; otherwise, participants would be penalized for volunteering to participate in the MCM research.

ii. Compensation for Research-Related Injury

Justice requires that children who participate in pediatric MCM research, which primarily aims to benefit other children and society more broadly, be treated or compensated for research-related injuries so that they do not bear a disproportionate share of the burdens of research. In addition, the principles of beneficence and respect for persons require that risks to participants be minimized; in this context, such risks include additional medical or financial harm resulting from research-related injuries. These ethical principles warranting treatment or compensation are particularly acute in the case of research-related injuries stemming from pre-event pediatric MCM research that is greater than minimal risk—children, who cannot legally or ethically consent to the research, are bearing greater risk than ordinarily permitted in order to potentially benefit future children in the event of a bioterrorism attack.¹⁷⁵

The argument that compensation for research-related injuries is not required because participants willingly accept the risk lacks force in the case of pediatric research.¹⁷⁶ Pediatric research participants are unable to provide valid informed consent, and therefore cannot fully accept the risks of research in the same way that adult research participants might. This fact weakens the argument that children enrolled in pre-event MCM research have waived any claim to care or compensation for research-related injuries by agreeing to participate.

Before approving pre-event pediatric MCM research under section 407, reviewers must ensure that researchers have assured that a plan is in place to treat or compensate injured pediatric research participants. The strong ethical obligation to provide care or compensation for injuries resulting from participation in pre-event MCM research entails providing injured research participants with needed medical care, including any available medications or interventions. Monetary compensation might also be necessary in the event of severe or long-term injury.

Although the likelihood of severe or long-term injury from pre-event MCM research is, under this framework, extremely low—particularly from interventions that have already been found safe in adults—the very assurance of compensation is both ethically and practically important.¹⁷⁷ (See Threshold of Acceptable Risk and Adequate Protection from Harm, Chapter 3.) It is important to note that compensation for research-related injuries, as discussed here, does not extend to incentives to participate in research. In pre-event pediatric MCM research, monetary reimbursement for costs outside of research-related injuries should be limited to reimbursement for participation costs, such as transportation and parking.

The Bioethics Commission reaffirmed its previous conclusion, noted in *Moral Science: Protecting Participants in Human Subjects Research*, that “subjects harmed in the course of human subjects research ought not individually bear the costs of care required to treat qualified harms resulting directly from that research.”¹⁷⁸ Particularly because of their vulnerable nature, children who enroll in pre-event pediatric MCM research, and become injured as a result of their participation, should be guaranteed all necessary medical care and appropriate compensation for such injuries.

Because this type of research is exceptional (and rare), the cost of compensation for research-related injuries is expected to be limited and would likely not require any major new federal infrastructure. As articulated in *Moral Science*, there is currently no overarching federal policy to ensure that injured research participants receive treatment or compensation.¹⁷⁹ However, there are some existing targeted federal programs, such as the National Vaccine Injury Compensation Program (NVICP) and the Covered Countermeasure Process Fund established by the PREP Act.¹⁸⁰

NVICP is the primary mechanism through which those injured by vaccines receive compensation in the United States. In the context of most MCMs, the NVICP is inadequate because the program only provides compensation for injuries resulting from vaccines listed in the Vaccine Injury Table or recommended by CDC for routine administration.¹⁸¹ Most vaccines used as MCMs are not listed on the Vaccine Injury Table. Accordingly, injuries caused by these MCMs would not be eligible for compensation under the NVICP. Moreover, not all MCMs are vaccines; MCMs can be any FDA-regulated product intended

to treat or prevent harm (or diagnose a condition) from the effects of chemical, biological, radiological, or nuclear attacks.

Children injured as a result of participating in MCM research will, however, have access to, but may be insufficiently protected by, the PREP Act. The PREP Act—passed to limit the liability of manufacturers, distributors, and others who develop, prescribe, administer, test, or dispense a countermeasure—provides limited access to compensation for those injured as a result of receiving an MCM.¹⁸² Individuals injured as a result of receiving an MCM can seek compensation through the “Covered Countermeasure Process Fund,” a pool of funds that comes into existence once the Secretary of HHS declares an emergency.¹⁸³ The PREP Act permits those who suffer “serious physical injury or death” to recover from the fund; those who suffer more minor injuries will be ineligible for compensation.¹⁸⁴ The PREP Act also establishes a statute of limitations of one year; injuries that manifest more than one year after administration are not entitled to compensation.¹⁸⁵ The Covered Countermeasure Process Fund is funded through congressional appropriations; it is unclear, however, whether Congress has ever appropriated funds.¹⁸⁶ As of December 2009, 24 letters of intent requesting benefits had been submitted under the PREP Act.¹⁸⁷ It is anticipated that any claims would be paid out of emergency appropriations.¹⁸⁸

Regardless of whether researchers rely on an established government mechanism, a system particular to the research funder, or a plan specific to a research site, they must ensure that a treatment and compensation plan is in place for any particular proposed study. The costs of any resulting harm or injury—whether or not it is severe—should not fall on child research participants or their families.

D. Community Engagement in Pre-event Research

The principle of democratic deliberation endorses respectful and inclusive collaborative decision making—a process that includes community engagement.¹⁸⁹ In the context of pre-event pediatric MCM research, engaging the community serves multiple ethical goals. The aims of community engagement include educating the public about the proposed research, providing relevant communities with opportunities to educate researchers about community-specific concerns, and encouraging community members to take advantage

of research products should the need arise. Community engagement helps build transparent, meaningful, collaborative, and mutually beneficial relationships among those considering or conducting research and the relevant communities.¹⁹⁰ Moreover, it helps to ensure that research is a joint enterprise, influenced by all relevant stakeholders, and that research is not directed solely by those who have a financial or professional interest in the results.

The process of community engagement is the responsibility of researchers, and should involve the public at every stage of research; address concerns and prevent unnecessary misgivings about the research; and strive to preempt any potential underuse of MCMs by the community in which they are tested. In the case of pre-event pediatric MCM research, community engagement is particularly important to address misgivings or mistrust because individual children within the community are exposed to risk for the potential benefit of other children in the community and the broader population. Community engagement in post-event research is discussed in greater detail below.¹⁹¹

In order for community engagement to be successful, researchers must identify key stakeholders.¹⁹² Stakeholders are individuals or groups who can influence or who are “affected by the conduct or outcome” of a biomedical research trial.¹⁹³ Examples of potential stakeholders in pediatric MCM research are illustrated in Figure 3.1. In the context of pediatric MCM research, relevant communities might be geographic—such as urban populations at potentially higher risk of a bioterrorism attack—or affiliated by special interests—such as first responders whose families might be the first to access MCMs in the event of an attack.

Once key stakeholders have been identified, researchers should engage them early and cooperate with them throughout the entire lifecycle of pre-event pediatric MCM research, from conceptualization through protocol development, execution, and communication of research results. Engaging marginalized communities along with the general public and other relevant stakeholders in the planning and conduct of this research will help to ensure ethical study design, implementation, and access to benefits should the need arise. The guidelines set forth in the Joint United Nations Programme on HIV/AIDS and the AVAC *Good Participatory Practice Guidelines* provide a useful framework for engaging relevant communities that might serve as a



Figure 3.1 Potential Stakeholders to Engage in Pediatric MCM Research

Adapted from: MacQueen, K.M., et al. (2012). Stakeholder Engagement Toolkit for HIV Prevention Trials. Washington, DC: FHI360, p. ix. Retrieved from <http://www.fhi360.org/sites/default/files/media/documents/StakeholderEngagementToolkitforHIVPreventionTrials.pdf>; Joint United Nations Program on HIV/AIDS. (2011). *Good Participatory Practices: Guidelines for Biomedical HIV Prevention Trials 2011, Second Edition*, p.14. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf

model in this context.¹⁹⁴ Alternatively, researchers might adopt the community advisory board model employed by the Framingham Heart Study or the HIV Vaccine Trials Network, which provides a forum for community member and research participant insight and input.¹⁹⁵

E. Transparency and Accountability

The review, approval, and conduct of pre-event pediatric MCM research that poses more than minimal risk should be transparent in order to enhance public accountability. As the Bioethics Commission recognized in *Moral Science*, “[i]nsufficient access to research information allows studies and results to be hidden and can result in injuries to human subjects, wasted resources, and unethical exposure to unnecessary risk.”¹⁹⁶ In keeping with the principles of democratic deliberation and beneficence, pre-event research that presents a minor increase over minimal risk and no prospect for direct benefit that is reviewed under section 407 should not be hidden from public view; rather, because it is fundamentally designed to benefit the public in the event of an unpredictable bioterrorism attack, and not to benefit directly the child participants, the Secretary should take special care to engage in robust and clear communications about pre-event pediatric MCM research projects. This research, which is conducted for the public good, should engage the public and remain transparent and accountable to them throughout the life of the project.

The Secretary should first ensure—as required by section 407—that there is adequate “opportunity for public review and comment” during the national-level review process, including the evaluation and communication of all anticipated risks and benefits that might be incurred in a proposed study. In making a decision to approve research, the Secretary should not rely solely on the advice of scientists, who might be predisposed to favor research, but should also consider the opinion of lay people, both as members of the 407 panel and as members of the public.

To achieve the goals of transparency and accountability, it is important to bear in mind that the appropriate composition of national-level review panels convened under section 407 will in itself provide a significantly influential means of community engagement and public accountability. By including several members of the public who do not harbor any specific bias, it is possible to reduce the likelihood that such panels might be compromised by

individuals who have conflicts of commitment or conflicts of interest, which include those financial, fiduciary, and other affiliations that might compromise the objectivity of, or public confidence in, the deliberative process. To avoid marginalizing community views, it is important that these panels include more than one community member and also recognize that not only the community members are expected to advocate for the interests of both research participants and the public good that is served by research.¹⁹⁷ All review panel members should be selected based on expertise and experience, which lends them independence—that is, a lack of vested interest in skewing the deliberations either toward or away from approval of a particular research protocol.

Moreover, after making a determination, the Secretary should publicly communicate the ethical rationale for approving or rejecting any pre-event pediatric MCM research proposal. Before proceeding with testing, the Secretary must provide clear communication of expected risks and benefits of the research. In addition, equally clear reasons must be publicly stated that justify the government ethically seeking the informed permission of parents and the meaningful assent of children to participate in this research.

Finally, throughout the study, the Secretary should provide periodic updates to and communication with the stakeholder communities and the U.S. public. (See Community Engagement in Pre-event Research, Chapter 3.) At the conclusion of the study, the study's findings should be made available to the public. Those community members who belong to a community directly affected by the research trial should be kept abreast of research results and have the opportunity to benefit from the understanding gained through participation and engagement with the researchers throughout the process.

* * *

All of these rigorous conditions are necessary to ensure that research approved under section 407 is conducted in accordance with “sound ethical principles.” These conditions, while necessary, are not sufficient. Informed parental permission and meaningful child assent also remain critical.

3. Are Adequate Provisions Made for Soliciting the Permission of Parents or Guardians and the Meaningful Assent of Children?

The third condition of section 407 requires that “adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians.”¹⁹⁸ Informed consent (or its moral equivalent) is a fundamental protection for research participants. Respect for persons requires that individuals be given the opportunity to make a voluntary, informed decision to participate in research to the extent they are able.¹⁹⁹ Although children are not legally competent to give consent, whatever level of partial autonomy they have must be respected and they must be given the “opportunity to choose to the extent they are able, whether or not to participate in research.”²⁰⁰ Researchers must not equate parental permission and child assent with the legal consent of adults.²⁰¹ Only competent adults have the legal authority to consent to participate in research or, in the context of research with children, to provide permission for their children to participate.²⁰²

An informed decision to permit one’s child to participate in research requires that parents understand specific information, including the purpose of the research, any risks and anticipated benefits, and alternative available protocols. Both parents and children should be given an opportunity to ask questions and should be informed that they may withdraw from the study at any time.²⁰³ Additionally, research participants and their parents must be informed of the extent to which confidentiality can be expected and should receive an explanation of the system in place to treat and provide compensation for any research-related injury or harm.²⁰⁴

Pediatric MCM research introduces additional layers of complexity to the informed consent process. Typical concerns about the quality of informed consent are magnified both by the fact that pediatric participants are not competent to consent, and by the heightened risks and uncertainties involved in MCM research. Researchers and persons independent of the research team whose responsibility it is to conduct the informed consent process for research studies must communicate these aspects of research to child participants in a developmentally appropriate manner.

Meaningful Assent. By definition, pediatric research involves participants who are legally and ethically unable to give valid consent due to their age; but where meaningful assent (or dissent) can be obtained, researchers should strive to include children in the decision making process. Although parental permission

is necessary for pediatric research, respect for persons requires that children, to the extent that they are able, also have the opportunity to express developmentally appropriate and meaningful assent (or dissent) to participation.²⁰⁵ Such assent does not have the ethical or legal standing of informed consent, but nevertheless acknowledges that children are developing the capacity to make autonomous decisions. The capacity of children to understand and meaningfully participate in research will vary widely with age and individual maturity. For example, some teenagers approaching the legal age of consent might be able to provide assent that approaches the ethical equivalent of adult consent.²⁰⁶ On the other end of the spectrum, researchers should not interpret the cries of an infant as an instance of meaningful dissent, even though a parent might reasonably see her child's distress as a reason to postpone participation or even to withdraw from the study. Ultimately, it falls to the informed judgment of parents as to whether to provide permission, but ethical research will include children in the process in a developmentally appropriate way.

It is essential that these differences in children's capacity for decision making be taken into account through the assent process. The purpose of seeking meaningful assent differs from that of seeking consent. Seeking meaningful child assent or dissent is an additional way of demonstrating respect for children as persons and enhances the open communication efforts of the research team.²⁰⁷ In addition, obtaining child assent reflects children's capacity (albeit limited) for self-determination and helps to foster the developing autonomy of children. Combined with parental permission (or denial of permission), meaningful assent (or dissent) can provide a substantive instance of the joint decision making characteristic of families.²⁰⁸ However, those evaluating a protocol also should ensure that assent procedures take into account empirical data reflecting differing views within families about the proper way to engage in shared decision making and should accommodate the possibility that including children in decision making can sometimes increase their levels of distress.²⁰⁹

Importantly, given the complexities involved in obtaining assent, meaningful assent cannot be assumed if the child fails to respond when asked. In addition, and consistent with current best practices, a child who meaningfully dissents, or does not agree to participate, should not participate. Parental permission cannot override a child's sustained meaningful dissent.²¹⁰

Practical Concerns. In order for parents and children to make a properly informed decision about whether to participate, the enrollment process must include educational materials that are appropriate for adults and children of various ages to ensure that both groups adequately understand the research. Materials should seek, for example, to inform potential pediatric participants about the study from the perspective of a child participant.²¹¹ Not only should the materials provided be developmentally appropriate, but the process of seeking parental permission and meaningful child assent in pre-event pediatric MCM research should be conducted by an independent person with expertise in developmentally appropriate child assent procedures. While an assent monitor is advisable in minimal risk pediatric MCM research, the employment of an independent person to obtain consent is imperative in pediatric MCM research that involves greater than minimal risk and no prospect of direct benefit. (See Pre-event Studies Posing No More Than Minimal Risk Approvable under Section 404, Chapter 3.)

To enable informed decision making, informational materials in the pediatric MCM context must both educate and communicate different and complex concepts that might not be communicated in typical biomedical research, including information about national security needs, the potentially unknown nature of the threat of an attack, and the public health requirements for the MCM under investigation. Particular attention must be paid to the perception of risks—both the inherent research risk borne by the participants, and the larger societal risk of a future attack necessitating the MCM research—and the entire process must be conducted in a way that ensures that there is not an illusory perception of a prospect of direct benefit on the part of either parents or children.

Reviewers are responsible for ensuring that researchers adequately describe and convey risk to those participating in a study. Given the complexity inherent in most MCM research, one means of ensuring that all the relevant information is clearly conveyed could be to present a video about the research to the participants and their parents, followed by an opportunity to ask questions.²¹² Research indicates that children demonstrate better understanding of study procedures and possible risks—and in some cases adults demonstrate better overall comprehension—when information is delivered in a multimedia format compared to the traditional written format.²¹³ Methods of conveying

protocol information should take into account the various ways individuals assimilate knowledge. Videos and investigators who explain the protocol should be drawn from diverse backgrounds and should look and sound like Americans from all parts of the country.²¹⁴ The independent person obtaining consent must be certain that parents and children understand that there will be no direct therapeutic benefit to a child participating in a pre-event MCM study. As appropriate, this person should ensure parent and participant comprehension by asking parents and children to demonstrate their understanding of these complex issues prior to enrollment in a study through simple and standardized assessments of understanding.

Various motivations affect the decision of parents to provide permission and children to provide meaningful assent. Motivations can include ethically reasonable influences such as altruism, developing a certain attitude in one's children, or even the desire to protect one's children by contributing to the development of a preventive intervention or therapeutic measure. With pediatric MCM research in particular, all involved should avoid using unduly influential rhetoric appealing to patriotism or to the responsibilities of "good parents" in the informed permission process. Those participating in pediatric MCM research should do so voluntarily, not in response to parental, social, or official pressure.

* * *

Taken together, the criteria discussed above provide the ethical content of the three conditions for 407 review relating to pre-event pediatric MCM research and specify ethical standards that must all be met in order for pre-event pediatric MCM research to proceed when risks are determined to reach a minor increase over minimal risk and there is no prospect for direct benefit.²¹⁵ Whether these criteria lead to approval or disapproval of proposed MCM research, they clarify what is at stake.

In circumstances in which it is impossible to comply with Recommendation 1—where possible, all pre-event pediatric MCM research be limited to minimal risk studies—the Bioethics Commission recommends the following:

Recommendation 4: Ethical Framework for National-Level Review of Pre-event Pediatric Medical Countermeasure Research

To ensure the thoroughness and ethical rigor of national-level review, reviewers should apply the Bioethics Commission's recommended ethical framework for reviewing pre-event pediatric medical countermeasure research that poses greater than minimal risk, but no more than a minor increase over minimal risk, under Department of Health and Human Services regulations at 45 C.F.R. § 46.407 and/or U.S. Food and Drug Administration regulations at 21 C.F.R. § 50.54. A proposed protocol must meet the requirements of the framework outlined in this report to be approved.

The framework clarifies the circumstances in which proposed research presents a "reasonable opportunity" to address a "serious problem," in particular, that seriousness must be judged by the consequences of exposure, likelihood (or threat) of exposure, and the "vital importance" of the information to be gained. The framework also specifies a rigorous set of conditions necessary to determine whether the research would be conducted in accordance with the required "sound ethical principles" that fall into five general categories: (1) ethical threshold of acceptable risk and adequate protection from harm; (2) ethical research design, for example, scientific necessity, valid research plan using small trials and age de-escalation with appropriate monitoring, and planning for post-event research; (3) post-trial requirements to ensure ethical distribution of medical countermeasures in the event of an attack, as well as a plan for treatment or compensation for research-related injury; (4) community engagement; and (5) transparency and accountability. Finally, the framework reiterates the importance of informed parental permission and meaningful and developmentally appropriate child assent.

Application to Trials of AVA with Children: No More Than a Minor Increase over Minimal Risk Pre-event Trials of AVA with Children

In confronting the ethical questions surrounding MCM testing in pediatric populations, the Bioethics Commission concluded that before ethical pre-event pediatric AVA trials can be considered, further steps must be taken, including additional minimal risk research with adult participants

to determine whether the research risks to children—who do not stand to benefit directly from it—pose no substantial risk to their health or well-being.

Given the amount of safety, immunogenicity, and dosing information about AVA in young adults aged 18 to 25 years, and given the widespread distribution of AVA in this population, it is possible that with additional testing in adults aged 18 to 20 years—testing to determine adverse effects, alternative dosing methods, and immunogenicity—testing of AVA with the oldest children (e.g., adolescents who are 16 to 17 years of age) could be considered no more than minimal risk. Consequently, it would be reviewed under section 404.

Informed, careful age de-escalation might allow researchers to infer minimal risk studies down the age scale. However, if data suggest that the use of AVA is affected, for example, by a child’s developmental stage (e.g., infancy or puberty), or if an inference of minimal risk from an older group of children to the next younger group is not possible, a study designed to pose a minor increase over minimal risk might be appropriate for national-level review.

The National Biodefense Science Board (NBSB) stated that, given the lack of data about AVA use by children, pre-event AVA research with children currently would “present more than a minor increase over minimal risk.”²¹⁶ Accordingly, pre-event AVA research with children as envisioned by NBSB would not be appropriate for national-level review or approvable under section 407 because this lack of data sets the level of risk beyond the acceptable threshold of a minor increase over minimal. Notably, NBSB considered research with children of all ages in making this determination. Inferring research risks from the youngest adults to children as a class (i.e., all persons 0 to 17 years of age), however, is considerably more difficult than doing so through careful age de-escalation. This is because young children differ developmentally in important ways from older children. Although extrapolation from adult data to research with children of all ages (i.e., 0 to 17 years of age) might not support an inference that all pediatric studies are minimal risk—or even a minor increase over minimal risk—age de-escalation along the lines outlined above might permit such an inference for AVA research with some pediatric age groups.

Post-event Studies

Public health officials must be prepared to conduct post-event research when a bioterrorism attack occurs regardless of whether pre-event pediatric MCM research trials were conducted.²¹⁷ In contrast to pre-event testing, in which ethical deliberations focus on whether any research with children would be ethically permissible, in post-event circumstances, research is ethically required to safeguard the well-being of current and future children. If a pediatric MCM research trial were completed pre-event, data should be collected following the administration of the tested intervention to acquire necessary additional safety information. In the absence of a pre-event investigation, an emergency situation might warrant administering an untested MCM to children in an effort to save lives. When children receive an untested MCM, it is ethically imperative that health officials collect data to learn as much as possible about the use of the untested MCM from the event.

In a post-event scenario, the ethical considerations of MCM research with children shift markedly.²¹⁸ Because of the increased likelihood that pediatric research participants have been exposed to an agent, and because exposed children will, in certain circumstances, be given an MCM under a treatment investigational new drug application (IND) (described in more detail below), the risks of research would be the risks of any additional observational procedures. Observational research might be minimal risk (approvable under section 404), or, given the potential to monitor and mitigate any adverse events related to the MCM, it might offer the prospect of direct benefit to individual research participants (approvable under section 405). Children exposed to a pathogen could also enroll in post-event research that is approvable based on its likelihood to yield information of vital importance to understanding or ameliorating the condition resulting from exposure (section 406).

Although different types of post-event studies could be approved under the current regulatory and ethical framework for pediatric research, there are inherent complexities in designing scientifically rigorous studies and streamlining the logistics of MCM distribution and administration after an emergency event. As set forth below, community engagement is one important tool that can help ensure the success of the research and uptake of the intervention within the affected community.

It is important to recognize that when the threat of an attack is imminent, the ethical and practical concerns surrounding proposed research track those of a post-event study even if technically conducted pre-event.²¹⁹ The Bioethics Commission's working definition of an imminent threat is that it is substantially certain to come about very soon and there is little to no time for deliberation or choice in action. These defining features of an imminent threat create conditions that are essentially similar, for both ethical and practical purposes, to post-event conditions. Critically, imminence should not be conflated with potential imminence. Imminence, by its very nature, means that there is no time for testing before moving to protect individuals as best as present knowledge permits. When an attack is imminent, research participants stand to benefit directly from the relevant research, or an identifiable class stands to benefit from the knowledge gained. In identifying the population affected by a determination of imminence (i.e., the bounds of the population that fits within the ethical review paradigm of post-event research), factors such as the type of attack, characteristics of the biohazardous agent, and intelligence regarding follow-up attacks should be considered.

In sum, although technically occurring before an attack, an imminent threat more closely resembles a post-event than a pre-event situation for all ethical and practical purposes because there would be no time to test an MCM with children before the attack occurs and children would be imminently at risk of exposure resulting from a specific threat. There is therefore no need to map new ethical terrain for the narrowly specified circumstances that characterize an imminent threat. Rather, the ethical landscape in such cases closely resembles the contours of post-event research. This report's ethical analysis and recommendations regarding post-event pediatric research, which follows, also applies to situations of imminent threat.

Ethical Issues in Post-event Research

Post-event (and imminent threat) pediatric MCM research is ethically distinct from pre-event research. The justification for such research no longer relies on a largely speculative societal benefit, but rests instead on more tangibly defined benefits that might accrue to children who have been exposed (or are about to be exposed) to an agent. Research with children who have been exposed could yield benefits to the identifiable class of children who are exposed to

the agent by producing vital knowledge about the resulting condition (section 406). Other children who have been exposed or are at risk of exposure might benefit directly by participating in post-event MCM research (section 405).²²⁰ Accordingly, post-event research is necessary both as a matter of beneficence (i.e., offering benefit to children) and justice in fulfilling society's obligation to secure the well-being of its most vulnerable citizens.

Because many children will have already received the MCM under investigation, post-event research will likely be limited to observational studies, involving various monitoring procedures and assessments to determine the function of the MCM when used by pediatric populations. Children who participate in a post-event MCM study approved under section 406 should be enrolled based on a determination that the research procedures present only a minor increase over minimal risk, that the intervention (in this case, monitoring procedures) presents experiences "reasonably commensurate" with what they would otherwise experience, and that the intervention is likely to yield generalizable knowledge of vital importance to understanding or ameliorating a condition caused by a chemical, biological, radiological, or nuclear agent used in a terrorism event.²²¹

When the monitoring procedures or care involved in research is expected to contribute to the well-being of individual participants by monitoring and mitigating adverse events, or a different procedure is expected to offer the prospect of direct benefit, such research might be approvable under section 405.²²² While treatment for a particular bioterrorism agent will generally be made available to all exposed children in any event, children who participate in research might nevertheless benefit from their participation to the extent a research protocol varies in a meaningful way from the care otherwise provided.

In the case of a public health emergency, IRB review of post-event research protocols will need to be swift to ensure that research can be conducted in a timely manner, which can be facilitated by thorough advanced preparation. FDA regulations allow for, and even encourage, pre-approval consultations that allow researchers to plan post-event trials, obtain pre-approval, and position their work for expedited review and approval in the event of an emergency.²²³ Reviewers must bear in mind, however, that post-event research occurs in an emergency setting, which creates distinct ethical challenges in

implementing a research protocol. While the review process might need to be modified for post-event research to be responsive to the immediacy of emergency conditions, it must still ensure that any protocol reviewed is held to the same high standards of ethical research conduct.²²⁴

“I don’t think it’s ever been done to have that type of a scaled [mass casualty] event in a rapid response situation with all the uncertainty, confusion, fear...and then, try on top of that to do a...clinical research protocol, however simple that protocol may be...[The idea is that] when parents bring their children for access to the vaccine, if they elect to have their child vaccinated,...as they’re coming out [of the mass vaccination site], they’re offered the opportunity to enroll their child in this nested protocol for reactogenicity and immunogenicity. [Compare that to] how smooth that [conversation with the parent] would go before an event, where you have the time to really sit down with the parent, to really talk about the vaccine, to really answer all those questions in a one-on-one situation with time for the parent to sit back and reflect on that before choosing to enroll their child. Or, [versus] being in a situation where their child has received the vaccine because they’ve potentially been exposed, and I’m [the parent] trying to save their life...and having to have that conversation in that situation.”

Maheer, C., Deputy Director, Office of Counter Terrorism and Emerging Threats, FDA. (2012). Regulatory Landscape for Providing MCMs to Children in an Emergency. Presentation to the Presidential Commission for the Study of Bioethical Issues, November 5. Retrieved from <http://bioethics.gov/cms/node/788>.

Certain ethical safeguards might be more difficult to implement in post-event research settings.²²⁵ For example, emergency circumstances might strain the process of informed parental permission and meaningful child assent.²²⁶ Nonetheless, provisions should be made to ensure that parents of potential child participants are adequately informed to make a reasonable decision regarding participation. Consent forms, for example, should be designed to be as simple and straightforward as possible without diminishing the essential information necessary to make truly informed decisions. Researchers and reviewers should take any potential complexities into account in advance of an event so that implementation of a post-event protocol is as straightforward as possible and research participants and their families are honored in accordance with respect for persons. IRBs reviewing post-event research protocols should ensure that an approved protocol incorporates special measures to assure that essential information is conveyed to parents of prospective participants and, when appropriate, to participants themselves.

Challenges in Post-event Research Design

In an emergency, children might be offered an MCM to protect them from the consequences of exposure, even when the safety and proper pediatric dosage for that MCM are incompletely or not at all characterized. If officials choose to administer an untested MCM in response to an attack, they can either dispense the MCM and collect limited data through a passive surveillance system (e.g., the Vaccine Adverse Event Reporting System) that relies on self-reporting of adverse events, or conduct a more active post-event study of the pediatric administration of the MCM.²²⁷

Because there are strict ethical limits to the risk permitted in exposing healthy children to an untested MCM, a pre-event trial would necessarily involve a limited number of participants and therefore the resulting data would also be limited. Whether post-event research is conducted as active or passive surveillance, such research can be larger in scope than pre-event studies and is likely to reveal additional data, for example, about adverse events, the immunogenicity of vaccine interventions, and possibly even efficacy. Given the larger sample size, researchers might be able to enroll and collect data from a diverse pool of children who receive the MCM, ensuring that any biological differences, including environmental interactions, among populations are accounted for in the event that another widespread distribution becomes necessary. Conducting such analyses will help to ensure that MCMs are safe for all children who receive them, fulfilling the dictates of justice—which requires that all children have equitable access to appropriate pediatric MCMs—and those of beneficence—which calls on those who provide the MCM to ensure that it is equally safe for all who receive it.

From a purely scientific perspective, there are also disadvantages to a post-event research approach.²²⁸ While a pre-event study can be a rigorous and systematic investigation that provides reliable data on various aspects of the intervention such as dosing requirements, a post-event study necessarily includes uncontrolled variables and might produce a more limited range of data or, worse, spurious associations leading to incorrect conclusions.²²⁹

The type and amount of data that can be obtained pre-event differs from that which can be documented post-event. Depending on how it is conducted, a pre-event pediatric MCM trial could provide immunogenicity data for vaccines,

dose-response curves (used to determine optimal dosing), evidence of the best administration method (e.g., subcutaneous or intramuscular injection, nasal spray, or liquid formulation), and adverse reaction data.²³⁰ Although a post-event study might yield useful logistical and distribution information to help shape future public health emergency responses, the clinical information that could reasonably be obtained in a post-event study likely would be general adverse reaction rates to the intervention, and, for vaccines, preliminary information about effectiveness and immunogenicity data.²³¹ With an IND, it might be possible to collect efficacy data, but such research likely would require more controlled data collection than is possible in an emergency. Information on

POST-EVENT RESEARCH COMPLEXITY

In accordance with current HHS plans, in the event of a mass anthrax spore release, both AVA and long-course antibiotics would be made available to children. In this setting, it would be difficult to isolate adverse event data from AVA alone, since antibiotics also have side effects. Adverse reactions to the treatment regimen might be attributable to antibiotics or to the vaccine, or an interaction between the two. Although these data would be imperfect, they would still provide information otherwise impossible to obtain without putting healthy children at risk. Additionally, since AVA is likely to only be used in combination with antibiotics in children, understanding the adverse events of the combination is valuable.

Sources: NBSB. (2011). *Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP): A Report of the National Biodefense Science Board*. Retrieved from <http://www.phe.gov/Preparedness/legal/boards/nbsb/recommendations/Documents/avwgrpt1103.pdf>; CDC. (2010). Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *Morbidity and Mortality Weekly Report Recommendations and Reports*, 59(RR-06), 1-30.

efficacy of an MCM will therefore always be limited, as it will be difficult to obtain post-event and it cannot be obtained pre-event because it would be unethical to intentionally expose anyone to a bioterrorism agent.²³²

In a post-event situation, the ability of researchers to control variables is constrained by the ethical imperative that—as a matter of justice and beneficence—researchers not restrict any child’s access to the best available care. With well-tested MCM distribution protocols in place, justice requires that all affected children have an equal opportunity to access the best available MCM care. Children who receive treatment in addition to the experimental MCM while enrolled in research might contribute data that would obscure the true effects of the MCM under investigation.²³³ For example, individuals might be provided with a long-acting measure to prevent future

infection (e.g., a vaccine) as well as a short-term therapy to prevent or treat immediate infection (e.g., antibiotics). The data from any post-event observational studies of this short-term and long-term combination therapy might conflate the cause of adverse reactions or efficacy between the two interventions. Differing levels of infection or illness might also complicate research results, as would pre-existing conditions or opportunistic infections unrelated to the bioterrorism attack.²³⁴ These might result in adverse events unrelated to the intervention, nonetheless, being misattributed to the intervention.²³⁵

Researchers must also ensure that those injured as a result of their participation in post-event research have access to necessary medical care and compensation for their injury. Some people who are injured as a result of receiving an MCM will have access to compensation under the PREP Act. (See Compensation for Research-Related Injury, Chapter 3.) Those who are injured by observational research procedures rather than by the MCM should similarly be entitled to compensation.

These design challenges underscore the need for investigators and reviewers to ensure that post-event research protocols are both scientifically valuable and valid. Such research can yield important, if limited, insights but cannot ethically proceed without a sound scientific design in place. By that same token, however, a strong post-event research framework does not obviate the need for appropriate and ethical pre-event research where possible.

Community Engagement in Post-event Research

To protect the population in the event of a bioterrorism attack, MCM research planning and implementation should include a robust system of community engagement (as discussed above) to keep the public apprised of research efforts and to enable democratic deliberation through active collaboration in its conduct.²³⁶ In particular, community engagement is critical to ensure that community members take advantage of an MCM in a post-event scenario when it is expected to prove beneficial. The obligation of community engagement falls to researchers who conduct post-event studies in collaboration with public health officials. The goals of community engagement—to educate the public about the research, allow the public to inform the researchers about its concerns and level of support for the research, and encourage the community to partake in the fruits of the research—are particularly salient in a post-event scenario.

Prior to an event, it will not be possible to identify all of the pertinent community stakeholders with an interest in post-event research. Nevertheless, generalized community engagement plans for the conduct of post-event research in a potential research community must be outlined before the research begins. Advance plans should include developing information for distribution, networking with community and faith-based organizations, and planning with local public health officials and agencies. General outreach strategies for disseminating information in an emergency should be established by researchers, as should specific measures to reach vulnerable populations that have difficulty engaging the health care system and groups that historically mistrust it. Post-event research planning should lay the groundwork for community engagement activities that can then be activated in the event of an attack.

After an event, the affected community can be defined and its specific concerns identified and addressed. Once an emergency occurs, or is determined to be imminent, location-specific post-event modifications of the more generalized plan, facilitated by local government, will be necessary to tailor the engagement effort to the affected community. Community engagement and outreach activities should begin immediately and must incorporate information on available MCMs—including both clinical details and accessibility—in addition to implementing research mechanisms.

While community consultation initiatives in a post-event environment undoubtedly will be complicated by other primary tasks, such as the distribution of therapeutic MCMs and addressing acute medical needs, it is important to seek the community's input, where possible, on the conduct of post-event MCM research. This can be done through public meetings or reaching out to local community organizations that are in regular contact with individuals and families. Although local community input might have only limited effect on the actual research design in a post-event scenario, collaboration can yield valuable information to guide participant recruitment, communicate with various groups in the community, and aid dissemination of research results. These measures might improve rates of use when an MCM is expected to prove beneficial and can encourage participation in follow-up research. A post-event scenario provides a unique opportunity to engage the community and

encourage participation since the emergency itself underscores the importance of having tested MCMs available when needed.

Recommendation 5: Post-event Pediatric Medical Countermeasure Research

Post-event research should be planned in advance and conducted when untested medical countermeasures are administered to children in an emergency or when limited pre-event medical countermeasure studies have already occurred. Institutional review boards must be cognizant of the exigencies imposed upon research under emergency conditions, and when reviewing post-event medical countermeasure research proposals, ensure that adequate processes are in place for informed parental permission and meaningful child assent. Institutional review boards must also ensure that the research design is scientifically sound, children enrolled in research have access to the best available care, adequate plans are in place to treat or compensate children injured by research, and provisions are made to engage communities throughout the course of research.

Authorizing Distribution of Unapproved Drugs in an Emergency

In the event of a bioterrorism attack, the U.S government has emergency preparedness plans to mobilize medical interventions, drugs, vaccines, and supplies from the Strategic National Stockpile for distribution to affected portions of the population. The federal government delivers supplies to the states, which have individualized distribution strategies based on localized need and infrastructure. In the event that the MCM needed is either still in clinical trials or has not yet been approved for the specified application, there are two mechanisms available—an emergency use authorization (EUA)

STRATEGIC NATIONAL STOCKPILE

The Strategic National Stockpile (SNS) is a national repository of medicine and medical supplies that can be rapidly distributed to the American public in the case of a public health emergency. Established in 2003 through the Homeland Security Act of 2002, the SNS includes vaccinations, antibiotics, antitoxins, antivirals, life support medications, and other surgical and medical supplies. As an extension of the 1999 National Pharmaceuticals Stockpile, the SNS is directly overseen and managed by HHS and CDC.

Source: CDC. (2012, October 15). Strategic National Stockpile (SNS) [Webpage]. Retrieved from <http://www.cdc.gov/phpr/stockpile/stockpile.htm/>.

and an IND—that allow the government to distribute an unapproved intervention to help people in an emergency. Underlying the motivation for these mechanisms are a host of ethical principles including respect for persons, beneficence, and justice. Together, the EUA and IND provide mechanisms to supply necessary MCMs with varying levels of clinical and research protections to ensure adequate respect for persons, as appropriate.

Emergency Use Authorization

There are times when the U.S. government might find that it has no FDA-approved drug in its arsenal to administer on a large scale to victims of a public health emergency. Alternatively, it might be the case that a prospectively safer or simpler pharmaceutical is in advanced development but has not yet received full FDA approval for an MCM application. In anticipation of these circumstances, Congress enabled FDA to authorize the use of unapproved products—or the unapproved use of approved products—in the event of a declared emergency, using an EUA.

The EUA is a tool for providing incompletely characterized but promising FDA-regulated interventions to the U.S. population in the event of an emergency. It is subject to very strict limitations. An EUA can be used only when the Secretary of HHS has declared an emergency justifying the unapproved use, and only when the emergency involves an agent that can cause a serious or life-threatening disease.²³⁷ In order to gain approval of an EUA, there can be no “adequate, approved, and available alternative” to the MCM under consideration, and, based on the totality of the evidence (including clinical trials when available), the Secretary must determine that it is “reasonable to believe that the product may be effective” in responding to the serious or life-threatening disease or condition caused by the agent or pathogen specified in the emergency declaration.²³⁸ Additionally, the known and potential benefits of using the authorized MCM must outweigh its known and potential risks.²³⁹ In considering and issuing an EUA, FDA advises the Secretary based on its assessment of a range of factors in the context of the declared emergency, including the possible risks of not receiving the candidate intervention.²⁴⁰ This process can be streamlined in the event of an emergency with an approved pre-EUA plan. A pre-EUA is submitted to FDA for “review prior to the determination of an actual or potential emergency in order to reduce

the time needed during an emergency to review the submission and consider authorization of the product.”²⁴¹

Importantly, the EUA is not a research tool. It allows for a drug or intervention to be given therapeutically but does not enable research on the intervention. The FDA Commissioner, however, can require that physicians and public health officials “collect and analyze safety and effectiveness data on the product” as a condition of the EUA.²⁴² In order to perform research, an IND would need to be in place. As such, research protections do not apply to those who receive an MCM authorized under an EUA. Respect for persons requires that very specific disclosure and consent requirements, as well as detailed instructions for its indications, accompany every EUA. But EUAs do not require as detailed an informed consent for administration as would investigational drugs in a research trial.²⁴³ This streamlined consent format is essential for the timely provision of MCMs in an emergency and is allowed because there must be minimal data in place before FDA will grant authorization for a drug to be used under an EUA. An EUA’s streamlined consent bypasses the heightened protections that usually apply when an unapproved drug (or unapproved indication of an approved drug) is administered in the research context.

FDA currently interprets the provisions of the EUA mechanism to require data from pediatric testing before an EUA can be issued for pediatric MCM use.²⁴⁴ The Bioethics Commission accepted the present interpretation of EUA requirements and agreed that it is preferable to reserve the use of the EUA mechanism for situations in which data are available to characterize the intervention in pediatric populations. Because children react to drugs and vaccines differently from adults, the heightened safeguards of pediatric research protections are appropriate for an intervention that is completely uncharacterized in children.

Investigational New Drug Application

Under FDA regulations, clinical investigation of a drug or biological product not previously approved for marketing in the United States requires submission of an IND.²⁴⁵

There are three types of INDs. An *investigator IND* (used most commonly in research involving interventions) is submitted by a researcher who initiates

and conducts an investigation of the investigational new drug. An *emergency use IND* authorizes a physician to obtain and use an experimental drug on a specific patient in extenuating circumstances under which there is not time to submit a full IND application, or to treat a patient that might not meet the requirements of the clinical trial protocol. The third type of IND, a *treatment IND*, allows for the use of a promising experimental drug in the treatment of patients not enrolled in a clinical trial while the final clinical work and FDA review take place.²⁴⁶

The IND mechanism was designed for use in planned clinical trials and may also be used to help individual patients in emergency situations.²⁴⁷ It was not designed for widespread distribution of a drug or intervention in the event of an outbreak or attack, and some have suggested that it is not well suited for this use. Those commentators have argued that the distribution of anthrax vaccine to postal workers as post-exposure treatment through an IND in 2001 demonstrated this inadequacy.²⁴⁸ However, in the case of a multi-state monkeypox outbreak in 2002, the distribution of smallpox vaccine to children through an IND is said to have been effective, and other scholars have maintained that studying the effects of certain other MCMs for children through an IND should not present significant challenges.²⁴⁹

Although the IND was not designed for emergency events, an investigational drug or intervention can be distributed under a treatment IND in an emergency. Consistent with beneficence, a treatment IND may be granted after FDA determines that:

- (1) The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
- (2) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and
- (3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.²⁵⁰

Similar to the pre-EUA mechanism, a pre-IND consultation can be arranged with FDA to assist in planning and expediting approval of the IND in the event of an emergency.²⁵¹

An investigator IND requires provision of extensive information about preclinical testing, any clinical testing that has already been performed, and any additional scientific or medical information characterizing the action of the intervention; so too must an investigator IND include assurance that trials will be conducted in adherence to human subjects protections and any other applicable FDA regulations.²⁵² After an IND is submitted, the investigator must typically wait 30 days before initiating a clinical trial while FDA reviews the IND for safety.²⁵³

In the event of an attack, and in the absence of pre-event pediatric MCM data, the appropriate MCM would be distributed, as a matter of respect for persons and beneficence, to children under a treatment IND with its host of research protections in place. An investigator IND should also be approved to study a small subset of those children, enrolled after they received the MCM through the treatment IND, in order to obtain more detailed information—such as immunogenicity and active surveillance data—from the pediatric administration of the MCM.²⁵⁴ Beneficence and non-maleficence call for research with a subset of the population to better understand the intervention in case future use is necessary.

Recommendation 6: Regulatory Mechanisms for Post-event Pediatric Medical Countermeasure Research and Distribution

When there are no data on the administration of a medical countermeasure to children and it will be provided to children in an emergency, the medical countermeasure should be provided under a treatment investigational new drug application (IND) to ensure that rigorous pediatric research protections apply to safeguard those children who receive the medical countermeasure. When a medical countermeasure is distributed broadly to children using a treatment IND, it is essential that the U.S. government also conduct a concurrent small-scale study under an investigator IND to obtain data that can potentially be used to support an emergency use authorization for pediatric use of the medical countermeasure in a future event. To expedite post-event research and ensure the availability of appropriate medical countermeasures

for children, a pre-IND consultation and approval should be put in place before an event.

Application to Post-event Trials of AVA with Children

In an event involving the release of weaponized anthrax, or other large-scale release of spores, a plan exists to provide children, like adults, treatment with a 60-day course of antibiotics as well as AVA.²⁵⁵ FDA and CDC have a treatment IND in place to allow for broad access to AVA for children in the event of an emergency. Work is ongoing to clarify the informed consent process. In addition, FDA and CDC are collaborating to develop a nested protocol that would involve research and surveillance to better understand immunogenicity and reactogenicity to the vaccine.²⁵⁶ Both of these mechanisms require IRB approval.

Under the Bioethics Commission's ethical approach, even if a pre-event study of AVA with children is approved, post-event research would be necessary to gather additional safety and immunogenicity data beyond the limited amount a pre-event study could produce. If a pre-event study is not approved and AVA is nonetheless administered to children in the event of an attack, post-event research would be ethically required.

In the event of a mass release of anthrax spores, FDA has authorized administration of AVA to adults using an EUA for post-exposure prophylaxis. (AVA is currently approved only for pre-exposure use by adults at risk for contracting anthrax.²⁵⁷) FDA requires pediatric data to support an EUA for pediatric use. In the absence of pre-event pediatric AVA research, AVA could not be distributed to children under an EUA. If pre-event pediatric research has been conducted, FDA would need to review the resulting data thoroughly and determine whether an EUA is warranted.

In the event of an anthrax attack, but in the absence of pre-event pediatric data, AVA will be available to children under a treatment IND. Beneficence requires that when an existing MCM can be expected to provide benefit, such an MCM should be made widely available. In this case, because AVA is expected to provide some benefit, it should be widely distributed under a treatment IND, allowing all parents to accept the vaccine for their child should they desire. This will ensure that, in accordance with respect for persons, the full force of pediatric research protections would govern its

distribution. In addition, any adverse event data from the administration of AVA to children would be collected through a passive surveillance system such as the Vaccine Adverse Event Reporting System.²⁵⁸

The nested IND (a combination of a treatment IND and an investigator IND) currently in place for AVA access also provides for active surveillance through an investigator IND of a subset of those who receive the vaccine. Because a treatment IND permits only limited collection of data, a proportion of children who receive the vaccine should also be enrolled in an active surveillance trial through an investigator IND. The subset of children and parents who agree to participate would do so only after a second thorough informed process that includes parental permission and meaningful child assent. Because this nested trial is an active surveillance trial rather than an intervention trial, the protocol would not entail any additional administration of the vaccine but might include procedures such as follow-up blood draws to study immunological response to the vaccine and ongoing communications to enable adverse reaction reporting.²⁵⁹ The information collected from this investigator IND active surveillance trial would provide baseline data about the use of AVA by children, and might make it possible to administer AVA more expeditiously to children through an EUA in the event of a future attack.²⁶⁰

There is an alternative structure to a nested, active surveillance trial: a “parallel” IND, in which a subset of exposed children would be enrolled through an investigator IND in a post-event trial to gather clinical data. These children would receive AVA through the trial rather than through the treatment IND, meaning that the dosage and administration of AVA could be varied. In addition to gathering safety and immunological response data, the trial would also evaluate dosing strategies. Although there are no regulatory barriers to such an approach, the nested IND is preferable because conducting dosing studies in a post-event setting risks under-immunizing children who have been exposed to anthrax. Moreover, conducting such studies would add logistical complications during an emergency situation, such as extending the length of time it takes to administer critical MCMs and impairing the adequacy of informed consent.

It is important that any post-event distribution of AVA to children, regardless of the specific mechanism, entail democratic deliberation in the form of extensive

community engagement. Community engagement should begin in pre-event research and continue through post-event activities. Children and their families must be made aware of the factual basis on which AVA administration is justified, most particularly the scientific knowledge and clinical data that support the decision to distribute it without full FDA approval. The rationale for distribution must be clearly and forthrightly communicated to avoid misunderstandings and potential mistrust of government, health care providers, and the research establishment. Moreover, it is critical that any post-event research protocol be scientifically sound, have adequate processes in place to ensure informed parental permission and meaningful child assent, provide for adequate treatment or compensation for research-related injuries, and ensure that enrolled children have access to the best available care.

Conclusion

Safeguarding children is one of our nation's foremost obligations. The ethical conduct of pre- and post-event pediatric MCM research is one way to fulfill our duty to protect children both as individual research participants and as members of society to the greatest extent possible in the event of an attack.

Pediatric research that presents no prospect of direct benefit to participants or that is not likely to yield generalizable knowledge about the participants' condition generally can only be conducted if it presents no more than minimal risk, except in extraordinary circumstances. Thus, the Bioethics Commission concluded that pre-event pediatric MCM research—which presents no prospect of direct benefit because no children are affected by the condition being studied—generally cannot proceed unless it is minimal risk research. Pre-event research might in some cases be designed in a way that would permit it to be judged minimal risk through an age de-escalation process in which risks are assessed and evaluated at each step. Robust research with young adults might support the conclusion that research with the oldest children is minimal risk. Similarly, research with the oldest children that further characterizes research risk might support an inference that research with the next oldest group of children is minimal risk as well.

Only when a minimal risk research design is not possible can proposed pre-event MCM research proceed to national-level review under section 407. Moreover,

pre-event MCM research can proceed only if it presents no more than a minor increase over minimal risk, and is conducted in accordance with the strict guidelines offered in this report. Under no circumstances should children be exposed to pre-event MCM research that poses substantial risk of serious illness or injury when there is no prospect of direct benefit to those children.

Critically, post-event research must be conducted when untested or minimally tested MCMs are administered to children in an emergency. Unlike pre-event MCM research, post-event MCM research might present a prospect of direct benefit to participants or be likely to yield generalizable knowledge about the participants' condition. Nevertheless, post-event studies should be minimal risk if possible, and incorporate robust research protections for pediatric participants. Emergency situations also present logistical complications, and responses that enable the conduct of post-event research should be prepared ahead of time to the extent possible with these ethical considerations in mind.

Pediatric MCM research brings into sharp focus the fact that the health and security of children are paramount. It highlights the importance of both protecting children from unjustifiable research risks and assuring their safety as far as possible in the event of an emergency. Grounding its work in the principles of respect for persons, beneficence, justice, and democratic deliberation, the Bioethics Commission reaffirmed the ethical foundations of pediatric research and applied them to the particularly complex and difficult case of pediatric MCM research. As exemplified by the Bioethics Commission's deliberations, such research warrants an ongoing national conversation in order to ensure the highest standards of protection for children that reflect an unwavering commitment to safeguard all children *from* unacceptable risks in research and *through* research that promotes their health and well-being.

ENDNOTES

- ¹ For the purposes of this report, the Bioethics Commission defined medical countermeasures (MCMs) as U.S. Food and Drug Administration (FDA)-regulated products and interventions used to combat the effects of chemical, biological, radiological, or nuclear (CBRN) events. Given the Bioethics Commission's definition of MCM, it used the term bioterrorism to refer to chemical, biological, radiological, and nuclear attacks generally.
- ² Letter from Secretary Kathleen Sebelius, Health and Human Services (HHS), to Amy Gutmann, Chair, Presidential Commission for the Study of Bioethical Issues (PCSB). (2012, January 6). p. 1. Retrieved from [http://bioethics.gov/cms/sites/default/files/news/Pediatric Countermeasures Letter from the Secretary.pdf](http://bioethics.gov/cms/sites/default/files/news/Pediatric%20Countermeasures%20Letter%20from%20the%20Secretary.pdf).
- ³ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1977). *Research Involving Children* (DHEW Publication OS 77-0004). Washington, DC: Department of Health, Education, and Welfare, p. 140. Retrieved from http://bioethics.georgetown.edu/pcbe/reports/past_commissions/Research_involving_children.pdf.
- ⁴ The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. (1978). *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (DHEW Publication OS 78-0012). Washington, DC: Department of Health, Education, and Welfare. Retrieved from <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html>.
- ⁵ The language of the two sets of regulations is substantively identical. The Bioethics Commission refers only to HHS regulations in the text of this report, although the discussion encompasses the provisions of Subpart D as codified by both HHS and FDA. See Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9,814 (March 8, 1983) (codified at 45 C.F.R. §§ 46.401 et seq.); Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589 (April 24, 2001) (codified at 21 C.F.R. §§ 50.50 et seq.).
- ⁶ In the case of FDA-regulated research, the Commissioner of Food and Drugs, in consultation with a national panel of experts makes the final determination (21 C.F.R. § 50.54). When research is governed by both FDA and HHS regulations, the Secretary of HHS makes the final determination. FDA. (2006, December). Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors: Process for Handling Referrals to FDA Under 21 C.F.R. 50.54. Retrieved from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf>.
- ⁷ U.S. Centers for Disease Control and Prevention (CDC). (2010). Use of anthrax vaccine in the United States: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *Morbidity and Mortality Weekly Report: Recommendations and Reports*, 59(RR-06), p. 21. Retrieved from <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5906a1.htm>; National Biodefense Science Board (NBSB). (2011). *Challenges in the Use of Anthrax Vaccine Adsorbed (AVA) in the Pediatric Population as a Component of Post-Exposure Prophylaxis (PEP): A Report of the National Biodefense Science Board*, p. 18. Retrieved from <http://www.phe.gov/Preparedness/legal/boards/nbsb/recommendations/Documents/avwvrpt1103.pdf>.
- ⁸ Maher, C., Deputy Director, Office of Counterterrorism and Emerging Threats, FDA. (2012). Regulatory Landscape for Providing MCMs to Children in an Emergency. Presentation to PCSBI, November 5. Retrieved from <http://bioethics.gov/cms/node/788>.
- ⁹ Letter from Secretary Kathleen Sebelius to Amy Gutmann, op cit.
- ¹⁰ The National Commission, (1978), op cit.
- ¹¹ For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Ethical Grounding, and Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407.
- ¹² For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Ethical Grounding, and Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Post-event Studies.
- ¹³ For a more detailed discussion of the definition of minimal risk (with some specific examples) see Chapter 2: Current Ethical and Regulatory Framework for Pediatric Research – Section 404: Minimal Risk Research, and Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Ethical Threshold of Acceptable Risk and Adequate Protection From Harm.

- ¹⁴ The National Commission, (1977), op cit.
- ¹⁵ *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.102; *Protection of Human Subjects*, FDA. 21 C.F.R. § 50.3.
- ¹⁶ NBSB, op cit, pp. 4-5.
- ¹⁷ Prescription Drug Products: Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure), 66 Fed. Reg. 55,679 (Nov. 2, 2002); Vietri, N.J. et al. (2006). Short-course postexposure antibiotic prophylaxis combined with vaccination protects against experimental inhalation anthrax. *Proceedings of the National Academy of Sciences*, 103(20), 7813-7816.
- ¹⁸ CDC, (2010), op cit. ACIP's analysis takes into account AVA's safety profile in adults and the advantages that vaccination can be expected to provide over long-term antibiotic use alone. Friedlander, A.M., et al. (1993). Postexposure prophylaxis against experimental inhalation anthrax. *The Journal of Infectious Diseases*, 167(5), 1239-1242; Klinman, D.M., et al. (2009). Anthrax prevention and treatment: Utility of therapy combining antibiotic plus vaccine. *Expert Opinions in Biological Therapies*, 9(12), 1477-1486; Vietri, N.J., et al. (2006). Short-course postexposure antibiotic prophylaxis combined with vaccination protects against experimental inhalational anthrax. *Proceedings of the National Academy of Sciences*, 103(20), 7813-7816.
- ¹⁹ CDC, (2010), op cit; NBSB, op cit. It is worth noting that the ACIP recommendation existed prior to both Dark Zephyr (in 2011) and the NBSB recommendation for pre-event research (also in 2011).
- ²⁰ Letter from Nicole Lurie, Assistant Secretary, Preparedness and Response, HHS, to Patricia Quinlisk, Chair, and Members, NBSB. (2011, April 27). p. 2. Retrieved from <http://www.phe.gov/Preparedness/legal/boards/nbsb/meetings/Documents/nbsbltr42711.pdf>.
- ²¹ *Ibid*, pp. 1-2.
- ²² NBSB, op cit, p. 40.
- ²³ *Ibid*, p. 25.
- ²⁴ *Ibid*, pp. 37-40.
- ²⁵ Letter from Secretary Kathleen Sebelius to Amy Gutmann, op cit.
- ²⁶ Given the Bioethics Commission's definition of MCM, it used the term bioterrorism to refer to chemical, biological, radiological, and nuclear (CBRN) attacks generally. In broad terms, MCMs are pharmaceutical products and other products used to prevent or mitigate the health effects of a CBRN event; large-scale natural disaster; or naturally occurring, emerging infectious disease. This general definition can be narrowed either by specifying the types of responses used to prevent and mitigate harm or by limiting the types of events that cause the harm in question. Various governmental agencies and policy centers have taken precisely this approach, narrowing the definition by, for instance, limiting MCMs to products, such as vaccines and antibiotics, used in response to CBRN events. *Project Bioshield Act of 2004*. 42 U.S.C. §§ 247d-6a(a)(2)(A), 247d-6b(c)(1)(B); *Pandemic and All-Hazards Preparedness Act*. 42 U.S.C. §§ 247d-7e(a)(4), (5), (7); see also *Public Readiness and Emergency Preparedness (PREP) Act*. 42 U.S.C. § 247d-6d(i)(1). The PREP Act describes "countermeasures" to "mean[] a drug (as that term is defined by section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1))), biological product (as that term is defined by section 351(i) of this Act (42 U.S.C. 262(i))), or device (as that term is defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(h)))." Other organizations have broadened the term to include therapeutic responses to natural disasters and emerging infectious diseases, such as H5N1 influenza virus and SARS. Biomedical Advanced Research and Development Authority (BARDA), HHS. (2011). *BARDA Strategic Plan 2011-2016*. Retrieved from <http://www.phe.gov/about/barda/Documents/barda-strategic-plan.pdf>. Although some definitions of MCM include non-FDA-regulated products and/or products used in response to naturally occurring outbreaks, the Bioethics Commission adopted a narrow definition for the purposes of this report.
- ²⁷ Under pediatric human subjects protections adopted by HHS and FDA, research protocols involving pediatric subjects may be approved at the local level if they fall within the following risk-benefit profiles (and meet other regulatory requirements): (1) pose only minimal risk to research participants (45 C.F.R. § 46.404; 21 C.F.R. § 50.51), (2) pose greater than minimal risk but offer a prospect of direct benefit to research participants (45 C.F.R. § 46.405; 21 C.F.R. § 50.52), (3) pose no more than a minor increase over minimal risk and offer the prospect of generating vitally important knowledge about a participant's condition (45 C.F.R. § 46.406; 21 C.F.R. § 50.53).

- ²⁸ This report references research regulated by 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54 as research with healthy children that poses more than minimal risk with no prospect of direct benefit, but recognizes that the research approvable under this mechanism may include subjects with conditions and other risk classifications. See Chapter 2: Current Ethical and Regulatory Framework for Pediatric Research – Current Regulations for Conducting Pediatric Research. Importantly, there are instances in which research involving a prospective MCM, but not conducted for MCM purposes, can be performed in circumstances that present a prospect of direct benefit to participants; for example, research with broad spectrum antibiotics or interventions well-characterized for use in other circumstances.
- ²⁹ The National Commission recommendation of how to review such proposed research was codified in pediatric research protection regulations at 45 C.F.R. § 46.407 (HHS) and 21 C.F.R. § 50.54 (FDA). The National Commission, (1977), op cit, p. 126.
- ³⁰ The evaluation of pediatric research posing greater than minimal risk but offering no prospect of direct benefit has been discussed to varying extents by several national bioethics commissions. The National Bioethics Advisory Commission (NBAC) noted that although its report on human subjects protections did not specifically address research with children, “special attention should be given to the ethical standards and regulatory requirements associated with providing adequate protections to children.” NBAC. (2001). *Ethical and Policy Issues in Research Involving Human Participants: Volume I*. Bethesda, MD: NBAC, p. 39. Retrieved from <http://bioethics.georgetown.edu/nbac/human/overvol1.pdf>. The Advisory Committee for Human Radiation Experiments (ACHRE) called for work to resolve the “controversial, unresolved issues” in “research with patients in the midst of a potential medical emergency” and “research involving children that may offer them no prospect of direct benefit but that may put them at greater than minimal risk, depending on how minimal risk is understood.” ACHRE also called for regulations to address the conduct of research involving institutionalized children, the variation in IRB performance, and clarification of the meaning of minimal risk in research with children. (Finding 22, Recommendation 11). ACHRE. (1995). *Final Report of the Advisory Committee on Human Radiation Experiments*. New York, NY: Oxford University Press. Retrieved from <http://www.hss.doe.gov/healthsafety/ohre/roadmap/achre/report.html>; See also National Human Research Protections Advisory Committee. (2001). *Children’s Workgroup Report*. Retrieved from <http://www.hhs.gov/ohrp/archive/nhrpac/mrg04-01/child-workgroup4-5-01.pdf>; Secretary’s Advisory Committee on Human Research Protections (SACHRP). (2005, April 18). Subcommittee on Research Involving Children: Recommendations Related to 45 C.F.R. § 46.404. Retrieved from <http://www.hhs.gov/ohrp/sachrp/sachrpltrtohssec.html>.
- ³¹ For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Pre-event Studies.
- ³² Klassen, T.P., et al. (2008). Children are not just small adults: The urgent need for high-quality trial evidence in children. *PLoS Medicine*, 5(8), 1180.
- ³³ Ibid, pp. 1180-1182; Stephenson, T. (2005). How children’s responses to drugs differ from adults. *British Journal of Clinical Pharmacology*, 59(6), 670-673.
- ³⁴ Environmental Protection Agency (EPA). (2005). Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants 2005. Retrieved from <http://www.epa.gov/raf/publications/pdfs/AGEGROUPS.PDF>.
- ³⁵ Bleicher, E.W.B. (2009). Encouraging research and development of pediatric medical devices through legislative and regulatory action: The Pediatric Medical Device Safety and Improvement Act of 2007 in context. *Food and Drug Law Journal*, 64(3), 531-564.
- ³⁶ Ibid.
- ³⁷ Anderson, M., Member and Fellow, American Academy of Pediatrics. (2012). Practical Challenges Posed by Pediatric Research. Presentation to PCSBI, May 17. Retrieved from <http://bioethics.gov/cms/node/709>; Thaul, S. (2007). *FDA’s Authority to Ensure that Drugs Prescribed to Children are Safe and Effective* (CRS Publication no. RL33986). Washington, DC: Congressional Research Service, p. 4. Retrieved from <http://www.fas.org/sgp/crs/misc/RL33986.pdf>.

- ³⁸ *Best Pharmaceuticals for Children Act*. 21 U.S.C. § 355a; *Pediatric Research Equity Act*. 21 U.S.C. § 355c. Both laws were reauthorized in the U.S. Food and Drug Administration Amendments Act of 2007. Pub. L. No. 110-85, 121 Stat. 823 (2007). They were amended in 2012 by the FDA Safety and Innovation Act. Pub. L. No. 112-144, 126 Stat. 993 (2012).
- ³⁹ Anderson, op cit. Over 425 labels were changed to include pediatric information as of October 2011. Institute of Medicine (IOM). (2012). *Safe and Effective Medicines for Children: Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act*. Washington, DC: National Academies Press. p. 34. Retrieved from <http://www.iom.edu/Reports/2012/Safe-and-Effective-Medicines-for-Children.aspx>.
- ⁴⁰ Ibid.
- ⁴¹ The National Commission, (1978), op cit; The National Commission, (1977), op cit; PCSBI. (2010, December). *New Directions: The Ethics of Synthetic Biology and Emerging Technologies*. Washington, DC: PCSBI, pp. 24-31; PCSBI. (2011, December). *Moral Science Protecting Participants in Human Subjects Research*. Washington, DC: PCSBI, pp. 96-101; PCSBI. (2012, October). *Privacy and Progress in Whole Genome Sequencing*. Washington, DC: PCSBI, pp. 27-31; NBAC. (1999). *Ethical Issues in Human Stem Cell Research*. Rockville, MD: NBAC. Retrieved from <http://bioethics.georgetown.edu/nbac/stemcell.pdf>; NBAC. (1997). *Cloning Human Beings*. Rockville, MD: NBAC. Retrieved from http://bioethics.georgetown.edu/pcbcl/reports/past_commissions/nbac_cloning.pdf; ACHRE. (n.d.) About the information contained in this gopher. Retrieved from <http://www.gwu.edu/~nsarchiv/radiation/dir/mstreet/about/intro.txt>.
- ⁴² *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.102; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.3; IOM. (2004). *The Ethical Conduct of Clinical Research Involving Children*. Washington, DC: National Academies Press.
- ⁴³ The National Commission, (1977), op cit.
- ⁴⁴ Council for International Organizations and Medical Sciences (CIOMS) and World Health Organization (WHO). (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Guideline 8, 14. Geneva: WHO; International Conference on Harmonisation. (1996, June). *Guideline for Good Clinical Practice E6(R1)*. Retrieved from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf; *Protection of Human Subjects, HHS*. 45 C.F.R. §§ 46.401 et seq; *Protection of Human Subjects, FDA*. 21 C.F.R. §§ 50.50 et seq; World Medical Association. (2008). *Code of Ethics of the World Medical Association: Declaration of Helsinki*. Ferney-Voltaire, France: World Medical Association.
- ⁴⁵ The National Commission, (1978), op cit.
- ⁴⁶ Beauchamp, T.L. (2005). The Origins and Evolution of the Belmont Report. In J.F. Childress, E.M. Meslin, and H.T. Shapiro. (Eds.). *Belmont Revisited: Ethical Principles for Research with Human Subjects* (pp. 12-25). Washington, DC: Georgetown University Press, pp. 15-16. For a similar debate on the conflation of autonomy and beneficence regarding pediatric research, see Miller, R.B. (2003). *Ethical Issues in Pediatric Research*. In *Children, Ethics, and Modern Medicine*. Bloomington, IN: Indiana University Press; Ramsey, P. (1970). *The Patient as Person*. New Haven, CT: Yale University Press.
- ⁴⁷ Mellanby, K. (1947). Medical experiments on human beings in concentration camps in Nazi Germany. *British Medical Journal*, 1(4490), 148-150.
- ⁴⁸ For more detail, see Appendix I: Sources of Pediatric Vulnerability.
- ⁴⁹ The phrase “essential interests” prescribes an analysis that focuses on those interests that are vital to an individual. It is distinct from a “best interests” assessment, which broadly encompasses all of an individual’s interests, regardless of gravity. Essential interests include one’s interests in life, health, bodily integrity, freedom from undue coercion, and freedom of expression. DeGrazia, D., Professor of Philosophy, George Washington University. (2012). *Special Considerations for Research with Children*. Presentation to PCSBI, May 17. Retrieved from <http://bioethics.gov/cms/node/708>.

- ⁵⁰ Redmon, R.B. (1986). How children can be respected as ‘ends’ yet still be used as subjects in non-therapeutic research. *Journal of Medical Ethics*, 12(2), 77-82. Redmon argues that the higher the risks and the less likely prospect for future societal benefit, the less plausible it is that the child would endorse participation in retrospect. Ibid.
- ⁵¹ *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.408; *Protection of Human Subjects*, FDA. 21 C.F.R. § 50.55; Emanuel, E.J., Wendler, D., and C. Grady. (2008). An ethical framework for biomedical research. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press, p. 126.
- ⁵² Of course, this is true of all decisions parents make on behalf of their children, such as how they are dressed or what schools they attend. This is part of how parents build the character of children—form them into members of families, cultures, religions, and societies—and help to make them, in part, who they are as persons.
- ⁵³ Grady, C. (2004). Ethics of vaccine research. *Nature Immunology*, 5(5), 465-468.
- ⁵⁴ Ramsey, P. (1970). Consent as a canon of loyalty with special reference to children in medical investigation. In P. Ramsey. (Ed.). *The Patient as a Person* (pp. 1-58). New Haven, CT: Yale University Press, pp. 11-12. Elsewhere, Ramsey acknowledges that research with children may be the lesser of two evils, that is when failing to do the research is also immoral. See Ramsey, P. (1976). The enforcement of morals: Nontherapeutic research on children. *The Hastings Center Report*, 6(4), 21-30; Marshall, M.F., Director, Program in Biomedical Ethics, Center for Biomedical Ethics and Humanities, Professor, Public Health Sciences, School of Medicine, and Professor, School of Nursing, University of Virginia. (2011). Anthrax Vaccine Trials in Children: Research and Risk in Mass Casualty Medicine. Presentation to PCSBI, November 5. Retrieved from <http://bioethics.gov/cms/node/781>.
- ⁵⁵ The National Commission, (1977), op cit; Dickert, N.W. (2009). Re-examining Respect for Human Research Participants. *Kennedy Institute of Ethics Journal*, 19(4), 311-338; Lysaught, M.T. (2004). Respect: Or, how respect for persons became respect for autonomy. *Journal of Medicine and Philosophy*, 29(6), 665-680; Lebacqz, K. (2005). We Sure Are Older But Are We Wiser? In J.F. Childress, E.M. Meslin, and H.T. Shapiro. (Eds.). *Belmont Revisited: Ethical Principles for Research with Human Subjects* (pp. 99-110). Washington, DC: Georgetown University Press.
- ⁵⁶ The National Commission, (1978), op cit; Miller, P.B., and N.P. Kenny. (2002). Walking the moral tightrope: Respecting and protecting children in health-related research. *Cambridge Quarterly of Healthcare Ethics*, 11(3), 217-229.
- ⁵⁷ The National Commission, (1978), op cit.
- ⁵⁸ Ibid.
- ⁵⁹ Ibid.
- ⁶⁰ PCSBI, (2010, December), op cit, p. 4.
- ⁶¹ The National Commission, (1978), op cit.
- ⁶² Ibid.
- ⁶³ Ibid. As stated in the *Belmont Report*, there are widely held justifications for unequal, but equitable distribution of research burdens and benefits.
- ⁶⁴ Emanuel, et al., (2008), op cit, p. 126.
- ⁶⁵ The National Commission, (1977), op cit, p. 132.
- ⁶⁶ PCSBI. (2010). Commission Deliberations and Public Comment. Meeting 3, Session 4, November 16. Retrieved from <http://bioethics.gov/cms/node/183>; Gutmann, A., and D. Thompson. (2004). *Why Deliberative Democracy?* Princeton, NJ: Princeton University Press; The National Commission, (1978), op cit; The National Commission, (1977), op cit; PCSBI, (2010, December), op cit, pp. 24-31; PCSBI, (2011, December), op cit.
- ⁶⁷ The National Commission, (1977), op cit.
- ⁶⁸ Ibid, p. xviii.

- ⁶⁹ Ibid.
- ⁷⁰ Ibid, pp. 127-128.
- ⁷¹ Ibid, pp. 140-141.
- ⁷² For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Community Engagement in Post-event Research, Pre-event Studies Posing No More Than a Minor increase over Minimal Risk Approvable under Section 407.
- ⁷³ The National Commission, (1977), op cit, p. 136.
- ⁷⁴ See Additional Protections for Children Involved as Subjects in Research, 48 Fed. Reg. 9,814 (March 8, 1983) (codified at 45 C.F.R. §§ 46.401 et seq.); Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589 (April 24, 2001) (codified at 21 C.F.R. §§ 50.50 et seq.) In 1979, FDA published proposed regulations and solicited comments in the *Federal Register*, but these regulations were never finalized and eventually FDA withdrew them in 1991. See Protection of Human Subjects; Proposed Establishment of Regulations, 44 Fed. Reg. 24,106 (Apr. 24, 1979) (to be codified at 21 C.F.R. pt. 50); Withdrawal of Certain Pre-1986 Proposed Rules, 56 Fed. Reg. 67,440 (Dec. 30, 1991). Although FDA formally adopted Subpart D in 2001, it had provided a number of safeguards to children even in the absence of special regulations: defining children as a vulnerable population for IRB review, providing information sheets with special provisions for parental permission and child assent, and encouraging investigators and IRBs to use HHS Subpart D as guidance for all research with children (see Additional Safeguards for Children, 66 Fed. Reg. 20,589). With congressional passage of the Pediatric Rule in 1998, which established a presumption of research with children and allowed FDA to require pediatric studies in certain products, and the FDA Modernization Act of 1997, which created economic incentives for pediatric product drug trials, the number of pediatric trials within FDA’s purview increased dramatically. FDA recognized a growing need for additional safeguards, which was reinforced by the Children’s Health Act, in which Congress mandated that “all research involving children that is conducted, supported, or regulated by HHS to be in compliance with 45 C.F.R. part 46, Subpart D” within six months of enactment (see Additional Safeguards for Children, 66 Fed. Reg. 20,589); *Children’s Health Act of 2000*. 42 U.S.C. § 289. In compliance with the Children’s Health Act, FDA adopted the language of HHS Subpart D as an interim rule with only minor modifications in language to tailor them to FDA’s regulatory authority.
- ⁷⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. §§ 46.40 et seq; *Protection of Human Subjects, FDA*. 21 C.F.R. §§ 50.1-3.
- ⁷⁶ Although other agencies might conduct pediatric clinical research, this report focuses on FDA and HHS regulations, which govern most of the clinical research conducted in the United States.
- ⁷⁷ *Protection of Human Subjects, HHS*. 45 C.F.R. §§ 46.401 et seq; *Protection of Human Subjects, FDA*. 21 C.F.R. §§ 50.50 et seq.
- ⁷⁸ Ibid.
- ⁷⁹ Ibid. Of note, when this responsibility falls to FDA alone, the determination is made by the Commissioner of Food and Drugs rather than by the Secretary of HHS. *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54. For concurrent review under §§ 46.407 and 50.54, the Secretary makes the final determination. FDA. (2006, December). Guidance for Clinical Investigators, Institutional Review Boards, and Sponsors: Process for Handling Referrals to FDA Under 21 C.F.R. 50.54. Retrieved from <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127605.pdf>.
- ⁸⁰ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54.
- ⁸¹ This report uses HHS citations in text, recognizing that the discussion applies to both HHS and FDA regulations.
- ⁸² The National Commission, (1977), op cit.
- ⁸³ Ibid.
- ⁸⁴ Ibid, p. 137.

⁸⁵ Ibid.

⁸⁶ Ibid, pp. 2-3.

⁸⁷ Ibid, p. xx.

⁸⁸ IOM, (2004), op cit; Letter from Secretary's Advisory Committee on Human Research Protections (SACHRP) to Michael O. Leavitt, Former Secretary, HHS. (2005, July 28). SACHRP Chair Letter to HHS Secretary Regarding Recommendations. Retrieved from <http://www.hhs.gov/ohrp/sachrp/sachrplrttohssec.html>; The National Commission, (1977), op cit; National Human Research Protections Advisory Committee (NHRPAC). (2001). Final Report to NHRPAC from Children's Workgroup. Retrieved from <http://www.hhs.gov/ohrp/archive/nhrpac/documents/nhrpac16.pdf>; Marshall, E. (2000). Enforcers halt NIH study called less risky than outdoor play. *Science*, 290(5495), 1281; Wendler, D., et al. (2005). Quantifying the federal minimal risk standard. *Journal of the American Medical Association*, 294(7), 826-832; see generally, Ross, L.F. (2003). Do healthy children deserve greater protection in medical research? *Journal of Pediatrics*, 142(2), 108-112; see also Rossi, J., and R.M. Nelson. (2012). Is there an objective way to compare research risks? *Journal of Medical Ethics*, 38(7), 423-427; Fisher, C.B, Kornetsky, S.Z., and E.D. Prentice. (2007). Determining risk in pediatric research with no prospect of direct benefit: Time for a national consensus on the interpretation of federal regulations. *American Journal of Bioethics*, 7(3), 5-10.

⁸⁹ The National Commission concluded "[t]he acceptability of the risk presented by such an intervention should be determined in the same way that the acceptability of risk is determined for interventions that are applied in standard [medical] practice." The National Commission, (1977), op cit, p. 125.

⁹⁰ Ibid, pp. 125-126.

⁹¹ *Protection of Human Subjects, HHS. 45 C.F.R. § 46.405; Protection of Human Subjects, FDA. 21 C.F.R. § 50.52*; The National Commission, (1977), op cit, pp. 5-6.

⁹² *Protection of Human Subjects, HHS. 45 C.F.R. § 46.405; Protection of Human Subjects, FDA. 21 C.F.R. § 50.52.*

⁹³ Although the National Commission never directly defined the term, it generally referred to it as a benefit to the individual's "health or welfare." The National Commission, (1977), op cit; More recently, NBAC specifically defined the range of benefits an IRB could consider, including within the category of direct benefit, "clinically significant information that could be used to influence the care provided," "standard treatments or interventions as part of the research," and "access to experimental therapies that may improve the participant's health status." NBAC explicitly distinguished these benefits from what it termed "indirect benefits," (encompassing benefits such as social contact, sharing information with others, and personal satisfaction) and from "incentives and payments," which it explained were not benefits. NBAC, (2001), op cit, p. 73. Other scholars have written extensively on the use of altruism or contribution to an important project as a benefit justifying some degree of risk over minimal. King, N.M.P. (2000). Defining and describing benefit appropriately in clinical trials. *Journal of Law, Medicine, and Ethics*, 28(4), 332-343; Litton, P. (2012). A more persuasive justification for pediatric research. *American Journal of Bioethics*, 12(1), 44-46; Simon, C., et al. (2006). Altruistic discourse in the informed consent process for childhood cancer clinical trials. *American Journal of Bioethics*, 6(5), 40-47; Spriggs, M. (2006). Can children be altruistic research subjects? *American Journal of Bioethics*, 6(5), 49-50; Wendler, D. (2012). A new justification for pediatric research without the potential for clinical benefit. *American Journal of Bioethics*, 12(1), 23-31.

⁹⁴ The National Commission, (1977), op cit, p. 127.

⁹⁵ Ibid, pp. 126-127.

⁹⁶ Ibid, p. 127.

⁹⁷ Ibid.

⁹⁸ Ibid, p. 139.

- ⁹⁹ *Human Subjects Protection, HHS*. 45 C.F.R. § 46.406; *Human Subjects Protection, FDA*. 21 C.F.R. § 50.53. The appropriateness of research posing more than minimal risk without the prospect of direct benefit involving children who have a disease or condition remains a contested issue. Fisher, et al. (2007), op cit; Martin, R.A., and J.S. Robert. (2007). Is risky pediatric research without prospect of direct benefit ever justified? *American Journal of Bioethics*, 7(3), 12-15. There is ongoing uncertainty over the precise definition of “disease or condition,” including whether it should be broadly or narrowly interpreted and whether being “at risk” for an illness constitutes a “condition.” Some have argued that “disease or condition” may be interpreted narrowly, as only a fully expressed disease or disability, or broadly, to include anything associated with illness. Problems with narrow interpretations arise because they do not take into account the fact that “the boundaries between being ‘healthy,’ ‘at risk,’ and ‘having a disease’ often blur,” and a narrow vision may shut out vital research for preventive therapies. At the same time, broad interpretations create the possibility of considering race, ethnicity, age, economic status, or other factors as “conditions” that justify risky research when the scientific evidence for causality among these factors may be questionable; Kopelman, L.M. (2004). What conditions justify risky nontherapeutic or “no benefit” pediatric studies: A sliding scale analysis. *The Journal of Law, Medicine, and Ethics*, 32(4), 749-758. Although debate over the scope of “disease or condition” continues, most IRBs are able to administer the provision adequately, and have roundly rejected its application to particular children who, due to clinical factors, can be classified as “at risk” for a disease or condition. See, e.g., *Grimes v. Kennedy Krieger Institute, Inc.*, 782 A.2d 807 (Md. 29, 2001); Letter from Michael A. Carome, Director, Division of Compliance Oversight, HHS, to Michael M. Gottesman, Deputy Director for Intramural Research, National Institutes of Health (NIH). (2000, November 3). RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1000 Research Project: Population Differences in the Insulin Sensitivity, Resting Energy Expenditure, and Body Composition of Overweight Children and Children of Overweight Parents. Retrieved from http://www.hhs.gov/ohrp/detrnm_letters/nov00a.pdf.
- ¹⁰⁰ For example, “[c]hildren with major chronic conditions, such as cystic fibrosis, diabetes, and sickle cell disease, used to die before reaching the age of majority. Now many live well into adulthood.” Oberman, M., and J. Frader. (2003). Dying children and medical research: Access to clinical trials as benefit and burden. *American Journal of Law and Medicine*, 29(2-3), 301-317.
- ¹⁰¹ The National Commission, (1977), p. 140.
- ¹⁰² Ibid, pp. 140-141.
- ¹⁰³ Ibid, pp. 127-128, 140.
- ¹⁰⁴ Ibid, p. 11.
- ¹⁰⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54. [Emphasis added].
- ¹⁰⁶ Proposed Regulations on Research Involving Children, 43 Fed. Reg. 31,786, 31,786 (July 21, 1978).
- ¹⁰⁷ Ibid.
- ¹⁰⁸ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54.
- ¹⁰⁹ Botkin, J.R., Consultant, Pediatric Advisory Committee, FDA. (2005). Presentation to the Pediatric Ethics Subcommittee, Pediatric Advisory Committee, FDA, November 15. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4178t1.pdf>.
- ¹¹⁰ “Healthy” in this context refers to individuals without the condition under investigation. While many children may have chronic conditions or transient infections, these illnesses do not necessarily interfere with their ability to act as controls in research. Unless a protocol involves no more than minimal risk, the inclusion of healthy individuals as controls cannot be approved under section 406 by a local IRB. Likewise, few of these protocols offer the prospect of direct benefit to healthy participants and thus cannot be approved under section 405. Protocols involving healthy controls have been the source of significant tension because, while the condition at issue might be very “serious,” it is rarely the type of exceptional situation for which the National Commission envisioned a need for nationwide public input and a justification for higher risk.

- ¹¹¹ See Appendix II: Summary of Pediatric Research Protocols Reviewed under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54 (1991-2012); see also e.g., Kopelman, L.M., and T.F. Murphy. (2004). Ethical concerns about federal approval of risky pediatric studies. *Pediatrics*, 113(6), 1783-1789; Ross, L.F. (2005). Lessons to be learned from the 407 process. *Health Matrix: Journal of Law-Medicine*, 15(2), 401-421. One reason for this low number of protocols undergoing 407 review is the fact that the FDA did not fully adopt the language of HHS Subpart D, with minor modifications, until the year 2000. Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589, 20,591 (Dec. 2, 1998). The number of cases reviewed and approved is still remarkably small, even if the time period considered is the past 12 years after the language was fully adopted.
- ¹¹² The National Commission, (1978), op cit; The National Commission, (1977), op cit, p. 140.
- ¹¹³ For more detail, see Chapter 1: Introduction – About this Report, and Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407.
- ¹¹⁴ The benefit referred to in section 405 is not limited to the benefits of an intervention, but includes as well the benefits of a “monitoring procedure likely to contribute to the subject’s well-being.” *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.405; *Protection of Human Subjects*, FDA. 21 C.F.R. § 50.52.
- ¹¹⁵ The Bioethics Commission recognized that in certain instances, when a threat is imminent, research carried out prior to the actual event might nevertheless be carried out more like post-event research (e.g., observational trials that are potentially approvable under section 405 because the imminence of the threat presents a situation where research participants stand to directly benefit).
- ¹¹⁶ For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Post-event Studies.
- ¹¹⁷ The National Commission, (1977), op cit, p. 140.
- ¹¹⁸ *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.404; *Protection of Human Subjects*, FDA. 21 C.F.R. § 50.51.
- ¹¹⁹ Regules, J.A., Cummings, J.F., and C.F. Ockenhouse. (2011). The RTS,S vaccine candidate for malaria. *Expert Review of Vaccines*, 10(5), 589-599; WHO. (2002). *Considerations Arising from Vaccine Trials Conducted in Paediatric Populations with High Disease Burden in Developing Countries: WHO/IVR Ethics Meeting, 26-28 November 2002, Accra, Ghana*. Geneva: WHO Department of Vaccines and Biologicals. Retrieved from http://whqlibdoc.who.int/hq/2004/WHO_V&B_04.04.pdf.
- ¹²⁰ Such has been the case for AVA, for example. Given the lack of pediatric data, the NBSB stated “the absence of data about the safety and immunogenicity of AVA in children does not support the conclusion that AVA administration presents no more than a minor increase over minimal risk.” NBSB, op cit, p. 24. The American Academy of Pediatrics made a similar finding, noting that, “given the possible risks,” any pre-event pediatric AVA study would fall under the ambit of 21 C.F.R. § 50.54/45 C.F.R. § 46.407. Anderson, op cit.
- ¹²¹ “Zero data and limited data are very different.” Berkelman, R. (2012). Medical Countermeasure Roundtable. Presentation to PCSBI, August 2. Retrieved from <http://bioethics.gov/cms/node/747>.
- ¹²² Berlin, C.M. (2009). Pharmacokinetics in Children [Webpage]. Retrieved from http://www.merckmanuals.com/professional/pediatrics/principles_of_drug_treatment_in_children/pharmacokinetics_in_children.html.
- ¹²³ Cieslak, T.J., and F.M. Henretig. (2003). Ring-a-ring-a-roses: Bioterrorism and its peculiar relevance to pediatrics. *Current Opinion in Pediatrics*, 15(1), 107-111.
- ¹²⁴ Sebastian, R.S., et al. (2010, September). What We Eat in America, NHANES 2005-2006: Fluid Milk Consumption in the United States. *Food Research Group Dietary Data Brief No. 3*. Retrieved from http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/DBrief/3_milk_consumption_0506.pdf.
- ¹²⁵ American Academy of Pediatrics. (2006). Chemical-biological terrorism and its impact on children. *Pediatrics*, 118(3), 1267-1278; Benavides, S., and M.C. Nahata. (2002). Anthrax: Safe treatment for children. *Annals of Pharmacotherapy*, 36(2), 334-337; Cieslak and Henretig, op cit.

- ¹²⁶ *Protection of Human Subjects*, HHS. 45 C.F.R. §§ 46.401 et seq.; *Protection of Human Subjects*, FDA. 21 C.F.R. §§ 50.50 et seq.
- ¹²⁷ FDA. (2012, May). BioThrax® (Anthrax Vaccine Adsorbed), p. 2. Retrieved from <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/UCM074923.pdf>.
- ¹²⁸ IOM. (2002). *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academies Press.
- ¹²⁹ Department of Defense. (n.d.). Anthrax Vaccine Immunization Program. Retrieved from <http://www.anthrax.osd.mil/vaccine/safe.asp>; IOM noted that, similar to other vaccines, there are sex differences in adverse reaction rates following administration of AVA and they recommended monitoring these differences in future studies. IOM, (2002), op cit; Niu, M.T., et al. (2009). VAERS Working Group: Adverse events after anthrax vaccination reported to the Vaccine Adverse Event Reporting System (VAERS), 1990-2007. *Vaccine*, 27(2), 290-297; Sever, J.L., et al. (2004). Safety of anthrax vaccine: An expanded review and evaluation of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Pharmacoepidemiology and Drug Safety*, 13(12), 825-840.
- ¹³⁰ CDC, (2010), op cit. See generally CDC. (2012). Vaccine Information Statements: Anthrax. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-anthrax.pdf>.
- ¹³¹ CDC. (2012). Vaccine Information Statements. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/>; CDC. (2012). Vaccine Information Statements: Anthrax. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-anthrax.pdf>; CDC. (2012). Vaccine Information Statements: Yellow Fever. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-yf.pdf>; CDC. (2012). Vaccine Information Statements: MMR. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-mmr.pdf>.
- ¹³² CDC. (2012). Vaccine Information Statements: Anthrax. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/downloads/vis-anthrax.pdf>.
- ¹³³ CDC. (2012). Vaccine Information Statements. Retrieved from <http://www.cdc.gov/vaccines/pubs/vis/>; CDC, (2010), op cit.
- ¹³⁴ *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.102; *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.404.
- ¹³⁵ CDC, (2010), op cit, p. 8; IOM, (2002), op cit; Marano, N., et al. (2008). Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: A randomized trial. *Journal of the American Medical Association*, 300(13), 1532-1543.
- ¹³⁶ Ivins, B.E., et al. (1996). Efficacy of a standard human anthrax vaccine against *Bacillus anthracis* aerosol spore challenge in rhesus monkeys. *Salisbury Medical Bulletin*, 87(Suppl), 125-126; Fellows, P.F., et al. (2001). Efficacy of a human anthrax vaccine in guinea pigs, rabbits, and rhesus macaques against challenge by *Bacillus anthracis* isolates of diverse geographical origin. *Vaccine*, 19(23-24), 3241-3247; Pitt, M.L., et al. (2001). In vitro correlate of immunity in a rabbit model of inhalational anthrax. *Vaccine*, 19(32), 4768-4773.
- ¹³⁷ Vietri, et al., (2006), op cit; Friedlander, et al., (1993), op cit.
- ¹³⁸ Brachman, P.S., et al. (1962). Field evaluation of a human anthrax vaccine. *American Journal of Public Health*, 52(4), 632-645; CDC, (2010), op cit, p. 9; Friedlander, A.M., Grabenstein, J.D., and P.S. Brachman. (2012). Anthrax Vaccines. In S.A. Plotkin, et al. (Eds.). *Vaccines*, 6th Edition, Edinburgh: Elsevier/Sanders, p. 136.
- ¹³⁹ CDC, (2010), op cit.
- ¹⁴⁰ FDA. (2006). Guidance for Industry: Development of Preventive HIV Vaccines for Use in Pediatric Populations. Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074819.htm>; Guinovart, C., and P.L. Alonso. (2007). Methods for determining vaccine efficacy and effectiveness and the main barriers to developing a fully deployable malaria vaccine. *Defining and Defeating the Intolerable Burden of Malaria III: Progress and Perspectives: Supplement to American Journal of Tropical Medicine and Hygiene*, 77(6), 278-281; Lell, B., et al. (2009). A randomized trial assessing the safety and immunogenicity of AS01 and AS02 adjuvanted RTS,S

- malaria vaccine candidates in children in Gabon. *PLoS ONE*, 4(10), e7611; *Pediatric Research Equity Act*. 21 U.S.C. § 355c; WHO, (2002), op cit.
- ¹⁴¹ FDA, (2006), op cit.
- ¹⁴² Nelson, S., Senior Pediatric Ethicist and Lead Medical Officer, Office of Pediatric Therapeutics, Office of the Commissioner, FDA. (2012). Presentation to PCSBI. May 17. Retrieved from <http://bioethics.gov/cms/node/708>.
- ¹⁴³ CDC, (2010), op cit.
- ¹⁴⁴ The National Commission, (1977), op cit, p. 139.
- ¹⁴⁵ For more detail, see Chapter 1: Introduction – About This Report, and Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Ethical Grounding.
- ¹⁴⁶ If the research is solely under FDA purview, the Commissioner of Food and Drugs will make this determination, rather than the Secretary of Health and Human Services. If the research is subject to both FDA and HHS regulation (i.e., because it is funded by HHS and regulated by FDA), then the review is conducted jointly by the agencies and the Secretary of HHS makes the final decision. *Protection of Human Subjects Research, FDA*. 21 C.F.R. § 50.54; *Protection of Human Subjects Research, HHS*. 45 C.F.R. § 46.407.
- ¹⁴⁷ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54.
- ¹⁴⁸ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407 [Emphasis added]; see also *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54.
- ¹⁴⁹ Ibid.
- ¹⁵⁰ Much of this assessment will prove pathogen-specific. For additional details on the specific vulnerabilities of children to various threat agents, see Appendix III: Characteristics of Category A Biological Agents.
- ¹⁵¹ For further discussion of the implications of imminence, see Chapter 3: Current Ethical and Regulatory Framework for Pediatric Research – Post-event Studies.
- ¹⁵² Changes in formulation or virulence of an agent will also significantly and independently affect the value of proposed MCM research.
- ¹⁵³ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.406; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.53.
- ¹⁵⁴ To avoid improper optimism or research bias, the determination that research is likely to yield important knowledge should be determined not just by scientists, but by lay members of the reviewing panel as well.
- ¹⁵⁵ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54. Although the regulations present no further guidance as to what constitutes “sound ethical principles,” the National Commission pointed to the Belmont principles of respect for persons, beneficence, and justice in its original recommendation, and specified additional principles that ought to apply. “The Commission believes that only research of major significance, in the presence of a serious health problem, would justify the approval of research under Recommendation (6)(B). The problem addressed must be a grave one, the expected benefit should be significant, the hypothesis regarding the expected benefit must be scientifically sound, and an equitable method should be used for selecting subjects who will be invited to participate. Finally, appropriate provisions should be made for assent of the subjects and permission and participation of parents or guardians.” The National Commission, (1977), op cit, p. 12.
- ¹⁵⁶ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.404; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.51.
- ¹⁵⁷ The National Commission, (1977), op cit, p. 139.

- ¹⁵⁸ Fleischman, A., Clinical Professor, Department of Pediatrics, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Yeshiva University. (2012). Ethical and Practical Considerations in 407 Review of Pediatric Research. Presentation to PCSBI, November 5. Retrieved from <http://bioethics.gov/cms/node/781>.
- ¹⁵⁹ Anderson, op cit; The National Commission, (1978), op cit.
- ¹⁶⁰ The National Commission, (1978), op cit.
- ¹⁶¹ Emanuel, E.J., Abdoler, E., and L. Stunkel. (n.d.). Research Ethics: How to Treat People Who Participate in Research, National Institutes of Health (NIH). Retrieved from http://www.bioethics.nih.gov/education/FNIH_BioethicsBrochure_WEB.PDF; Emanuel, E.J., Wendler, D., and C. Grady. (2000). What makes clinical research ethical? *Journal of the American Medical Association*, 283(20), 2701-2711; Shevell, M. (2002). Ethics of clinical research in children. *Seminars in Pediatric Neurology*, 9(1), 46-52.
- ¹⁶² FDA. (2011). Ensuring the Safety of Vaccines in the United States [Webpage]. Retrieved from <http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM298181.pdf>; Michael, N., Director, U.S. Military HIV Research Program. (2013). Presentation to PCSBI, January 15. Retrieved from <http://bioethics.gov/cms/node/816>; IOM. (1993). *The Children's Vaccine Initiative: Achieving the Vision*. Washington, DC: National Academies Press, p. 109-127. Retrieved from http://www.nap.edu/openbook.php?record_id=2224&page=114; WHO, (2002), op cit.
- ¹⁶³ WHO, (2002), op cit.
- ¹⁶⁴ CIOMS and WHO, (2002), op cit; The National Commission, (1977), op cit.
- ¹⁶⁵ Strictly speaking, the concept of “overall benefit to children as a class” here considers not only expected benefit but also any relevant risks such as risks of adverse reactions to the use of MCMs.
- ¹⁶⁶ In the event of an emergency, MCMs that are unapproved can be distributed in accordance with mechanisms that will be considered in detail in Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Post-event Studies.
- ¹⁶⁷ Emanuel, et al., (2000), op cit.
- ¹⁶⁸ Ibid.
- ¹⁶⁹ Shevell, (2002), op cit.
- ¹⁷⁰ PCSBI, (2011, December), op cit, p. 82.
- ¹⁷¹ Lockwood, B., 1st Vice President, USA Council of International Association of Emergency Managers. (2012). Medical Countermeasure (MCM) Distribution. Presentation to PCSBI, November 5. Retrieved from <http://bioethics.gov/cms/node/782> (“The single most frequently cited reason for [first responders] hesitating to report is lack of family protection.”); See also Walker, K., Program Manager, Emergency Services Coalition for Medical Preparedness. (2012). Comments submitted to PCSBI, September 11, 2012 (“Biological and chemical threats pose an universal, existential danger to all Americans, [and] the emergency services sector as the frontline require[s] special measures....Any plan to confront these threats cannot be considered complete without a strategy to ‘protect the protectors.’”).
- ¹⁷² Moore, T.A., Chairman, Department of Infectious Diseases, Ochsner Health System. (2012). Medical Countermeasure Roundtable Discussion. Presentation to PCSBI, July 9. Retrieved from <http://bioethics.gov/cms/node/747>.
- ¹⁷³ This plan might draw on extant distribution strategies and should include acquisition to the Strategic National Stockpile (SNS), like other products the U.S. government plans to use for pediatric populations in an emergency.
- ¹⁷⁴ To ensure an adequate supply, systems must be in place for rapid scale-up procedures and preparation for production and storage of the MCM in the event research concludes the MCM is appropriate for pediatric use. Hodge, J., Lincoln Professor of Health Law and Ethics, Sandra Day O'Connor College of Law, Arizona State University. (2012). Special Considerations for Medical Countermeasure Research and Use. Presentation to PCSBI, May 17. Retrieved from <http://bioethics.gov/cms/node/710>; Kaplowitz, L.J., Deputy Assistant

- Secretary for Policy, Director, Office of Policy and Planning, Office of the Assistant Secretary for Preparedness and Response, HHS. (2012). Special Considerations for Medical Countermeasure Research and Use. Presentation to PCSBI, May 17. Retrieved from <http://bioethics.gov/cms/node/710>.
- ¹⁷⁵ This is not to say, however, that other contexts do not warrant treatment or compensation for research-related injuries. The Bioethics Commission reaffirms its endorsement of treatment and compensation for qualified harms resulting directly from research, as first set forth in *Moral Science*. PCSBI, (2011, December), op cit, pp. 62-70.
- ¹⁷⁶ Hope, T. (1997). Compensating subjects of medical research. *Journal of Medical Ethics*, 23(3), 131-32 (arguing that compensation is not justified when research participants consent to risks). However, this view is overbroad, and does not apply in case of pediatric research. Fleischman, A.R., and L. K. Collogan. (2008). Research with children. In E.J. Emanuel, et al. (Eds.). *The Oxford Textbook of Clinical Research Ethics*. New York, NY: Oxford University Press.
- ¹⁷⁷ As a practical matter, individuals might be less willing to enroll children in pre-event pediatric MCM research conducted under section 407 if they are left unprotected in the event of injury, but, practical considerations aside, the ethical considerations provide sufficient reason to mandate compensation.
- ¹⁷⁸ PCSBI, (2011, December), op cit, p. 62.
- ¹⁷⁹ Ibid, p. 64.
- ¹⁸⁰ Health Resources and Services Administrations, HHS. (n.d.). National Vaccine Injury Compensation Program. [Webpage]. Retrieved from <http://www.hrsa.gov/vaccinecompensation/index.html>; *PREP Act*. 42 U.S.C. §§ 247d-6d(i)(1).
- ¹⁸¹ The Office of Special Masters, U.S. Court Of Federal Claims. (2004). Guidelines for Practice Under The National Vaccine Injury Compensation Program. Retrieved from <http://www.usfc.uscourts.gov/sites/default/files/OSM.Guidelines.pdf>.
- ¹⁸² *PREP Act*. 42 U.S.C. §§ 247d-6d(i)(1); *Targeted Liability Protections for Pandemic and Epidemic Products and Security Countermeasures*. 42 U.S.C. §§ 247d-6d; Liu, E.C. (2010). *Pandemic Flu and Medical Biodefense Countermeasure Liability Limitation*. Washington, DC: Congressional Research Service, p. 4. Retrieved from <http://www.fas.org/sgp/crs/misc/RS22327.pdf>.
- ¹⁸³ *Covered Countermeasures Process*. 42 U.S.C. §§ 247d-6e; *Targeted Liability Protections for Pandemic and Epidemic Products and Security Countermeasures*. 42 U.S.C. §§ 247d-6d; Liu, (2010), op cit, p. 4. (A declaration for anthrax has been in effect since October 1, 2008); *Targeted Liability Protections for Pandemic and Epidemic Products and Security Countermeasures*. 42 U.S.C. §§ 247d-6d.
- ¹⁸⁴ *PREP Act*. 42 U.S.C. §§ 247d-6d(i)(1).
- ¹⁸⁵ Ibid.
- ¹⁸⁶ *Countermeasures Injury Compensation Program (CICP): Administrative Implementation*, HHS. 42 C.F.R. pt. 110.
- ¹⁸⁷ HHS. (2010). Justification of Estimates for Appropriations Committees, p. 394. Retrieved from <http://www.hrsa.gov/about/pdf/budgetjustification2011.pdf>.
- ¹⁸⁸ Ibid.
- ¹⁸⁹ For more detail, see Chapter 2: Current Ethical and Regulatory Framework for Pediatric Research – Development of the Central Tenet of Pediatric Research, Democratic Deliberation. See also The National Commission, (1978), op cit; The National Commission, (1977), op cit; PCSBI, (2010, December), op cit, pp. 24-31; PCSBI, (2011, December), op cit, pp. 96-101; PCSBI, (2012, October), op cit, pp. 27-31.
- ¹⁹⁰ Joint United Nations Program on HIV/AIDS. (2011). *Good Participatory Practices, Guidelines for Biomedical HIV Prevention Trials 2011, Second Edition*. Retrieved from http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf.

- ¹⁹¹ For more detail, see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Post-event Studies, Community Engagement in Post-event Research.
- ¹⁹² Joint United Nations Program on HIV/AIDS, op cit.
- ¹⁹³ Ibid, p. 14; Horowitz, C.R., Robinson, R.M., and S. Seifer. (2009). Community-based participatory research from the margin to the mainstream: Are researchers prepared? *Circulation*, 119(19), 2633-2642.
- ¹⁹⁴ Joint United Nations Program on HIV/AIDS, op cit.
- ¹⁹⁵ Community advisory boards, when used, are generally stipulated for every site at which a study is conducted and provide a means for community members and research participants to provide insight and feedback on the proposed research design and methods. For further information on the Framingham Heart Study Ethics Advisory Board, see The Framingham Heart Study. (2013). About the Framingham Heart Study [Webpage]. Retrieved from <http://www.framinghamheartstudy.org/about/index.html>. For further information on the community advisory boards of the HIV Vaccine Trials Network, see the HIV Vaccine Trials Network. (n.d.). Community Advisory Board (CAB). Retrieved from <http://www.hvtn.org/community/cab.html>. See also Community Recommendations Working Group of Community Partners and NIAID. (2009). Recommendations for Community Involvement in National Institute of Allergy and Infectious Diseases HIV/AIDS Clinical Trials Research. Retrieved from http://www.hvtn.org/community/CAB_Recommendations_Certified.pdf (describing the requirements for community advisory boards in certain NIH-funded trials); Woodsong, C., and Q. A. Karim. (2005). A model designed to enhance informed consent: Experiences from the HIV Prevention Trials Network. *American Journal of Public Health*, 95(3), 412-419.
- ¹⁹⁶ PCSBI, (2011, December), op cit, pp. 47-48.
- ¹⁹⁷ IRB membership criteria might also inform 407 panel composition. The membership requirements of IRBs are established by *Institutional Review Boards, FDA*. 21 C.F.R. § 56.107 and *IRB membership, HHS*. 45 C.F.R. § 46.107; See also Recommendations 3.9 and 3.10 of the NBAC's 2001 report. NBAC, (2001), op cit; DeVries, R., and C.P. Forsberg. (2002). Who decides? A look at ethics committee membership. *HEC Forum*, 14(3), 252-258; Schuppli, C.A., and D. Fraser. (2007). Factors influencing the effectiveness of research ethics committees. *Journal of Medical Ethics*, 33(5), 294-301; Speers, M.A., and S. Rose. (2012). Commentary: Labeling institutional review board members does not lead to better protections for research participants. *Academic Medicine*, 87(7), 842-844.
- ¹⁹⁸ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.407; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.54.
- ¹⁹⁹ The National Commission, (1978), op cit.
- ²⁰⁰ Ibid; See also Young, W.F., President, The Endocrine Society. (2012). Comments submitted to PCSBI, August 23, 2012 ("IRBs [should] avoid viewing children of all ages as equal in cognition and critical thinking capabilities. Older children and adolescents should be viewed with the potential for higher levels of understanding and self-determination.").
- ²⁰¹ For the purposes of this report, the Bioethics Commission refers both to parents and legal guardians when it used the word "parent."
- ²⁰² *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.116; *Protection of Human Subjects, HHS*. 45 C.F.R. 46 § 46.408; Diekema, D.S. (2006). Conducting ethical research in pediatrics: A brief historical overview and review of pediatric regulations. *The Journal of Pediatrics*, 149(Suppl.1), S3-11; Kodish, E. (2003). Informed consent for pediatric research: Is it really possible? *The Journal of Pediatrics*, 142(2), 89-90.
- ²⁰³ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.116; The National Commission, (1978), op cit.
- ²⁰⁴ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.116.
- ²⁰⁵ The National Commission, (1977), op cit, p. 129; The National Commission, (1978), op cit.
- ²⁰⁶ Even where not recognized by law, mature adolescents may generally be perceived as at least as capable of understanding the ramifications of their choices, and of exercising self-determination, as their less wise counterparts who happen to be 18 years of age.

- ²⁰⁷ Joffe, S. (2003). Rethink “affirmative agreement,” but abandon “assent.” *The American Journal of Bioethics*, 3(4), 9-11; Wendler, D., and S. Shah. (2003). Should children decide whether they are enrolled in nonbeneficial research? *The American Journal of Bioethics*, 3(4), 1-7; Wilfond, B.S., and D.S. Diekema. (2012). Engaging children in genomics research: Decoding the meaning of assent in research. *Genetics in Medicine*, 14(4), 437-443.
- ²⁰⁸ Miller, V.A., and R.M. Nelson. (2006). A developmental approach to child assent for nontherapeutic research. *The Journal of Pediatrics*, 149(1Suppl), S25-S30.
- ²⁰⁹ Brody, J.L., et al. (2003). Voluntary assent in biomedical research with adolescents: A comparison of parent and adolescent views. *Ethics and Behavior*, 13(1), 79-95; Snethen, J.A., et al. (2006). Family patterns of decision-making in pediatric clinical trials. *Research in Nursing and Health*, 29(3), 223-232; Varma, S., Jenkins, T., and D. Wendler. (2008). How do children and parents make decisions about pediatric clinical research? *Journal of Pediatric Hematology/Oncology*, 30(11), 823-828; Wendler and Shah, op cit, p. 4.
- ²¹⁰ *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.402(b). There are two possible exceptions to requiring participant assent: First, when the research offers a prospect of direct benefit to participants that is otherwise unattainable with existing alternatives. This exception does not apply in the case of research reviewed under section 407. Second, taking into account the age, maturity, and psychological state of potential participants, an IRB determines that participants are not competent to reasonably be consulted. *Protection of Human Subjects*, HHS. 45 C.F.R. § 46.408(a). On the differing standards for dissent and assent, see Murphy, T.F. (2003). Assent and dissent in 407 research with children. *The American Journal of Bioethics*, 3(4), 18-19; Wendler, D.S. (2006). Assent in paediatric research: Theoretical and practical considerations. *Journal of Medical Ethics*, 32(4), 229-234; Wendler and Shah, op cit, p. 6.
- ²¹¹ Fleischman, op cit.
- ²¹² Ibid.
- ²¹³ O’Lonegan, T.A., and J.E. Forster-Harwood. (2011). Novel approach to parental permission and child assent for research: Improving comprehension. *Pediatrics*, 127(5), 917-924.
- ²¹⁴ Fleischman, op cit.
- ²¹⁵ See Appendix IV: An Ethical Framework to Guide National-Level Review of Pediatric Medical Countermeasure Research under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54.
- ²¹⁶ NBSB, op cit, p. 25.
- ²¹⁷ Given the Bioethics Commission’s definition of MCM, as FDA-regulated products and interventions used to combat the effects of CBRN events, the post-event research discussion is focused on MCMs employed in response to a CBRN event. Much of what is discussed, however, can be applied more broadly to interventions used in response to any public health emergency.
- ²¹⁸ This section primarily addresses the ethical considerations of post-event MCM research with children. However, ethical concerns can emerge in other aspects of bioterrorism planning and response as well, especially in the clinical realm, involving, for example, triage, the distribution and allocation of supplies, and informed consent to treatment. See, e.g., Berg, J., and N. King. (2006). Strange bedfellows? Reflections on bioethics’ role in disaster response planning. *The American Journal of Bioethics*, 6(5), 3-5; Holloway, H.C., et al. (1997). The threat of biological weapons: Prophylaxis and mitigation of the psychological and social consequences. *Journal of the American Medical Association*, 278(5), 425-427; Moreno, J. (2002). Bioethics After the Terror. *American Journal of Bioethics*, 2(1), 60-64; Pesik, N., Keim, M.E., and K.V. Iserson. (2001). Terrorism and the ethics of emergency medical care. *Annals of Emergency Medicine*, 37(6), 642-645; Sutton, V. (2005). A multidisciplinary approach to an ethic of biodefense and bioterrorism. *The Journal of Law, Medicine, and Ethics*, 33(2), 310-322; Thewes, J., Fitzgerald, D., and D.P. Sulmasy. (1996). Informed consent in emergency medicine: Ethics under fire. *Emergency Medicine Clinics of North America*, 14(1), 245-254. To the extent that these complexities constrain the conduct of researchers, they ought to inform the design and implementation of post-event research. They are also deserving of distinct ethical consideration for those developing guidelines for disaster preparedness and emergency clinical practice—topics that lie outside the purview of this report.
- ²¹⁹ For more detail, see Chapter 1: Introduction, and see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Ethical Grounding.

- ²²⁰ It is also possible that post-event research could be minimal risk (approvable under 45 C.F.R. § 46.404) where the only intervention is observational research.
- ²²¹ *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.406; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.33.
- ²²² *Protection of Human Subjects, HHS*. 45 C.F.R. § 46.405; *Protection of Human Subjects, FDA*. 21 C.F.R. § 50.52.
- ²²³ *Investigational New Drug Application, Early Application, FDA*. 21 C.F.R. § 312.82.
- ²²⁴ Maher, op cit.
- ²²⁵ Chong, S., et al. (2010). Clinical research in times of pandemics. *Public Health Ethics*, 3(1), 35-38; IOM. (2011). *Advancing Regulatory Science for Medical Countermeasure Development: Workshop Summary*. Washington, DC: National Academies Press, pp. 69-70.
- ²²⁶ Biros, M.H., et al. (1995). Informed consent in emergency research: Consensus statement from the Coalition Conference of Acute Resuscitation and Critical Care Researchers. *Journal of the American Medical Association*, 273(16), 1283-1287; Quinn, S.C., Thomas, T., and S. Kumar. (2008). The anthrax vaccine and research: Reactions from postal workers and public health professionals. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 6(4), 321-333.
- ²²⁷ HHS. (2013, February 8). Vaccine Adverse Event Reporting System (VAERS) [Webpage]. Retrieved from <http://vaers.hhs.gov/index>; *Postmarketing Reporting of Adverse Experiences, FDA*. 21 C.F.R. § 600.80; *Investigational New Drug Application, FDA*. 21 C.F.R. pt. 312. For an illustration of the differences between active and passive surveillance, see Appendix V: Example of Difference between Passive and Active Surveillance Study.
- ²²⁸ NBSB, op cit.
- ²²⁹ Ibid.
- ²³⁰ Ibid.
- ²³¹ Bales, M.E., et al. (2002). Epidemiologic response to anthrax outbreaks: Field investigations, 1950–2001. *Emerging Infectious Diseases*, 8(10), 1163-1174; NBSB, op cit.
- ²³² This may not be the case if pathogens are naturally occurring in certain regions, which might make efficacy testing in those regions ethically possible.
- ²³³ NBSB, op cit.
- ²³⁴ Halsey, N.A., et al. (2012). Algorithm to assess causality after individual adverse events following immunizations. *Vaccine*, 30(39), 5791-5798.
- ²³⁵ Ibid.
- ²³⁶ For more detail, see Chapter 2: Current Ethical and Regulatory Framework for Pediatric Research – Development of the Central Tenet of Pediatric Research, Democratic Deliberation, and see Chapter 3: Ethical Considerations for Pediatric Medical Countermeasure Research – Pre-event Studies Posing No More Than a Minor Increase over Minimal Risk Approvable under Section 407, Community Engagement.
- ²³⁷ *Expanded Access to Unapproved Therapies and Diagnostics*. 21 U.S.C. § 360bbb-3.
- ²³⁸ Ibid.
- ²³⁹ Ibid.
- ²⁴⁰ Ibid.
- ²⁴¹ FDA. (2005, August 3). SOPP 8010: Administrative Procedures for Emergency Use Authorization of Medical Products. Retrieved from <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPs/ucm061226.htm>.

- ²⁴² FDA. (2007, July). Guidance-Emergency Use Authorization of Medical Products. Retrieved from <http://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm>.
- ²⁴³ Nightingale, S.L., Prasher, J.M., and S. Simonson. (2007). Emergency Use Authorization (EUA) to enable use of needed products in civilian and military emergencies, United States. *Emerging Infectious Diseases*, 13(7), 1046-1051.
- ²⁴⁴ Maher, op cit.
- ²⁴⁵ *Investigational New Drug Application, FDA*. 21 C.F.R. § 312.20. Although the IND process is the same for drugs and biologics, the process of approval for drugs and biologics is different. Drugs are approved by FDA through the New Drug Application, Abbreviated New Drug Application, and Over the Counter processes and biologics are approved through the Biologic Licensing Application process. FDA. (2010, September 21). Types of Applications [Webpage]. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/default.htm>.
- ²⁴⁶ FDA. (2011, June 6). Investigational New Drug (IND) Application [Webpage]. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>.
- ²⁴⁷ *Investigational New Drug Application, FDA*. 21 C.F.R. pt. 312.
- ²⁴⁸ Nightingale et al., op cit.
- ²⁴⁹ Halsey, N., Professor of International Health, Johns Hopkins Bloomberg School of Public Health and Professor and Pediatric Infectious Disease Physician, Department of Pediatrics, Johns Hopkins School of Medicine. (2012). Assessing Pediatric Research: Considering Individual Risk and Societal Benefit. Presentation to PCSBI, August 2. Retrieved from <http://bioethics.gov/cms/node/744>; Nelson, op cit.
- ²⁵⁰ *Investigational New Drug Application, FDA*. 21 C.F.R. § 312.305.
- ²⁵¹ *Investigational New Drug Application, FDA*. 21 C.F.R. § 312.82; FDA. (2011, June 6). Investigational New Drug (IND) Application [Webpage]. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>.
- ²⁵² *Investigational New Drug Application, FDA*. 21 C.F.R. pt. 312.
- ²⁵³ FDA. (2011, June 6). Investigational New Drug (IND) Application [Webpage]. Retrieved from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>.
- ²⁵⁴ Memorandum from Jason Gerson, Senior Officer, Innovate FDA, and Skip Nelson, Senior Pediatric Ethics, Office of Pediatric Therapeutics, FDA, to PCSBI. (2012, May 15). FDA Medical Countermeasures-Related Documents and Information.
- ²⁵⁵ CDC, (2010), op cit, p. 21; NBSB, op cit, p. 18.
- ²⁵⁶ Maher, op cit.
- ²⁵⁷ CDC, (2010), op cit; Maher, op cit.
- ²⁵⁸ HHS. (2013, February 8). Vaccine Adverse Event Reporting System (VAERS) [Webpage]. Retrieved from <http://vaers.hhs.gov/index>.
- ²⁵⁹ The 2002 IOM Report on AVA safety and efficacy distinguishes between active and passive surveillance trials, and describes the methods of several active surveillance trials. Those studies include blood draws to determine immunogenicity, as well as close communication between health care personnel and vaccine recipients to determine the presence of both local and systemic adverse events. IOM, (2002), op cit.
- ²⁶⁰ See Maher, op cit; Nelson, op cit.

APPENDICES

Appendix I: Sources of Pediatric Vulnerability

Although children might exhibit a range of vulnerabilities, the one most commonly associated with children is cognitive vulnerability. The chart below summarizes the much broader range of potential vulnerabilities that a child might experience.

TYPE OF VULNERABILITY	DESCRIPTION OF SOURCE OF VULNERABILITY
Incapacitational	Limits on the capacity to deliberate about and decide to participate in a study due to cognitive development and deliberative ability.
Juridic	Formal relationships of authority or power, often hierarchical, built into social structures. Especially noteworthy for children are the legal and parental authority of parents or guardians.
Deferential	Social and cultural pressures that socialize some into a willingness to comply with the desires of others, despite an inner reluctance. This may coincide with the relationships characteristic of juridic vulnerability.
Social	Entrenched prejudice and stereotypical thinking that compromises care and consideration due to children. Membership in a group whose rights and interests have been socially devalued.
Situational	Medical urgency or other forms of exigency create circumstances that remove or create obstacles to eliciting the education, deliberation, and decision making characteristic of informed consent and child assent.
Medical	Medical diagnoses or prognoses that alter a prospective participant's cost-benefit calculations to skew them toward taking risks they otherwise would think foolish.
Allocational	Social and accidental distribution of benefits and burdens that participation in research might exacerbate or exploit.

Adapted from: Kipnis, K. (2003). Seven vulnerabilities in the pediatric research subject. *Theoretical Medicine*, 24(2), 107-120.

Appendix II: Summary of Pediatric Research Protocols Reviewed under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54 (1991-2012)

Since 1991, 14 expert panels have been convened pursuant to 45 C.F.R. § 46.407 (and/or 21 C.F.R. § 50.54) to review pediatric research protocols. Of these protocols, 10 were approved, including 2 approved under 45 C.F.R. § 46.406 and another approved under 45 C.F.R. § 46.405 for the affected children involved and under 45 C.F.R. § 46.407 for the healthy child participants. Four research protocols were denied approval by national-level reviewers. One protocol was denied on the grounds that it lacked sufficient scientific justification and contained serious shortcomings with respect to informed consent, and because the *in vitro* and animal data were insufficient to justify the research in younger children prior to testing with older children. Two protocols were denied because there were insufficient data from adult trials to justify the work with children. Another protocol, a review of Dryvax (smallpox vaccine) research, was not approved because bioterrorism preparedness plans had evolved and the government no longer planned to use Dryvax for children.

PRIOR NATIONAL-LEVEL REVIEWS (1991-2012)

TITLE, YEAR	RESEARCH GOAL
Myoblast Transfer in Duchenne Muscular Dystrophy, 1991*	Characterize the effects of myoblast transfer in young children.
NIH Human Growth Hormone Protocol, 1992†	Test synthetic human growth hormone to determine whether it increases ultimate adult height.
Cognitive Function and Hypoglycemia in Children with Insulin-Dependent Diabetes Mellitus, 1993‡	Collect data on differences in children related to blood sugar. Proposal would test healthy children and children with Type I diabetes. Testing would involve infusing through two intravenous lines glucose and insulin at varying infusion rates to attain a specific blood glucose level.
Hyperglycemic and Euglycemic-Hyperinsulinemic Clamp Procedure (Subset of Larger Obesity Study halted by OHRP for review), 2000§	Monitoring obese or at risk for obesity children to understand genetic factors that affect body weight. Included in the protocol were blood draws, X-ray imaging, MRI abdomen scans, and the “clamp” procedure, involving an overnight hospital stay while intravenous catheters were inserted and used to infuse sugar and insulin.
Precursors to Diabetes in Japanese-American Youth, 2002¶	Study would enroll 300 healthy, non-diabetic children with some degree of Japanese descent and 150 healthy, non-diabetic children of Caucasian descent between the ages of 8 and 10 years and follow them for two years to observe factors that could contribute to diabetes development. Protocol involved physical examination, blood draw, intravenous glucose tolerance test, dual energy X-ray absorptiometry, and MRI to measure abdominal fat.
Alcohol, Sleep, and Circadian Rhythms in Young Humans, Study 2—Effects of Evening Ingestion of Alcohol on Sleep, Circadian Phase, and Performance as a Function of Parental History of Alcohol Abuse/Dependence, 2003#	Protocol would study the effects of a small or moderate evening dose of alcohol on sleep, waking performance, and circadian phase in adolescents and young adults, and examine how the effects may differ between individuals who have a parent with a history of alcohol dependence and those who do not. Study would give participants alcohol.
Characterizations of Mucus and Mucins in Bronchoalveolar Lavage Fluids from Infants with Cystic Fibrosis, 2003**	Proposed longitudinal study of the changes in bronchoalveolar lavage fluid of infants diagnosed with cystic fibrosis in the neonatal period. Researchers would perform bronchoscopies in infants diagnosed with cystic fibrosis in the first six weeks of life, at six months, and at one year. Control data would be obtained from children without cystic fibrosis who were undergoing bronchoalveolar lavage for other clinical indications.

* Proposed Protocol Entitled Myoblast Transfer in Duchenne Muscular Dystrophy; Recommendations, 56 Fed. Reg. 49189 (Sept. 27, 1991).

† NIH Human Growth Hormone Protocol Review Committee. (1992). *Report of the NIH Human Growth Hormone Protocol Review Committee*. Bethesda, MD: NIH.

‡ Cognitive Function and Hypoglycemia in Children with IDDM, 58 Fed. Reg. 40819 (July 30, 1993).

§ Marshall, (2000), op cit.

¶ Ross, L.F. (2004). Convening a 407 panel for research not otherwise approvable: “Precursors to diabetes in Japanese American youth” as a case study. *Kennedy Institute of Ethics Journal*, 14(2), 165-186.

REASON REFERRED TO 407 REVIEW PANEL	PANEL DECISION
Research involved risks “significantly greater than minimal” and offered no prospect of direct benefit to the individual children who were to be participants.	Not approved. The panel concluded that the proposed protocol lacked sufficient scientific justification and contained serious shortcomings with respect to informed consent. The panel found the protocol to be based on insufficient <i>in vitro</i> and animal data, and to lack justification for initiation in younger rather than older children.
Concerns raised by various nonprofit oversight groups and IRBs that use of placebo controls in these trials exposed children to unnecessary discomfort and psychosocial risks. Panel convened mid-study.	Approved. The panel concluded that the risks posed were no greater than a minor increase over minimal and with adequate disclosure about placebo and ongoing monitoring of the placebo group, including annual re-assent, the study complied with section 406.
Research involved greater than minimal risk and offered no prospect of direct benefit to the individual children who were to be the healthy control participants.	Approved. The panel concluded the protocol presented reasonable opportunity to further understanding of a serious condition affecting the health or welfare of children.
Research involved greater than minimal risk, offered no prospect of direct benefit, and proposed to enroll healthy children as participants.	Approved. The protocol was originally approved by the IRB as involving minimal risk, based on their assessment that the study was no more dangerous than “playing actively on sidewalks and streets.” The HHS Office for Human Research Protections (OHRP) halted the study, finding the IRB application of minimal risk outside the proper scope of the term. OHRP later permitted the study to proceed under a reinterpretation of the participants as having a condition by being at risk for developing Type 2 diabetes, and a finding that the research was no more than a minor increase over minimal risk (section 406).
Research involved greater than minimal risk, offered no prospect of direct benefit, and proposed to enroll healthy children as participants.	Approved. The panel concluded that it was an opportunity to further understanding of a serious condition affecting the health or welfare of children. One panel member dissented, arguing that design defects made the trial unlikely to yield useful information. It is unclear whether the protocol was ever employed.
Research involved greater than minimal risk, offered no prospect of direct benefit, and proposed to enroll healthy children as participants.	Not approved. The panel concluded that insufficient data existed for similar research in adult populations from which a decision about the risks and safety of the protocol could be made. OHRP allowed research to move forward in the population of individuals 21 to 22 years of age, noting that the resulting information could be used when the adolescent protocol was re-reviewed.
Research involved greater than a minor increase over minimal risk and offered no prospect of direct benefit to participants.	Approved. The panel concluded that it was an opportunity to further understanding of a serious condition affecting the health or welfare of children, but conditioned approval on certain protocol modifications to ensure that the protocol complied with sound ethical principles.

* Solicitation of Public Review and Comment on Research Protocol: Alcohol, Sleep, and Circadian Rhythms in Young Humans, Study 2—Effects of Evening Ingestion of Alcohol on Sleep, Circadian Phase, and Performance as a Function of Parental History of Alcohol Abuse/Dependence, 68 Fed. Reg. 17950 (April 14, 2003).

**Solicitation of Public Review and Comment on Research Protocol: Characterization of Mucus and Mucins in Bronchoalveolar Lavage Fluids from Infants with Cystic Fibrosis, 68 Fed. Reg. 35414, 35415 (June 13, 2003).

PRIOR NATIONAL-LEVEL REVIEWS (1991-2012)

TITLE, YEAR	RESEARCH GOAL
HIV Replication and Thymopoiesis in Adolescents, 2003*	Study to understand the premature aging of the immune system for individuals infected with HIV. Study proposed using healthy, HIV negative controls as well as individuals with HIV. Study would enroll individuals between the ages of 13 and 24 years and the protocol involved medical histories, physical exams, and computed tomography (CT) scans of the thymus. A subset of the study populations would receive glucose either intravenously or by the mouth and be monitored through blood draws.
Sleep Mechanisms in Children: Role of Metabolism, 2003†	In order to better understand the interaction of sleep and metabolism in children, the study would track glycogen content, glutamate turnover rate, and glutamate-glutamine cycling in wakefulness and sleep in children aged 13-17 years.
Multicenter Randomized Dose Response Study of the Safety, Clinical, and Immune Responses of Dryvax Administered to Children 2 to 5 Years of Age, 2003‡	Study would test a diluted form of Dryvax, a smallpox vaccine, in children between the ages of 2 and 5 years. The goal of the study was to determine whether the limited remaining supply of Dryvax, which was no longer being produced, could be stretched to protect more people by diluting the vaccine.
Effects of a Single Dose of Dextroamphetamine in Attention Deficit Disorder: A Functional Magnetic Resonance Study, 2004§	Protocol would administer a single 10 milligram dose of dextroamphetamine with concurrent functional magnetic resonance imaging (fMRI) to children between the ages of 9 and 18 years with attention deficit hyperactivity (ADHD) and normal controls. In addition to the fMRI, subjects would also submit to a screening MRI, neuropsychological testing, and basic health exam and medical history review, including pregnancy testing.
Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty, 2005¶	Study would investigate the quality of a new diagnostic procedure intended to better distinguish among causes of precocious puberty and delayed puberty in children and young adults. Investigators planned to administer in healthy children and children with disorders of puberty a single dose of leuprolide acetate and measure hormonal response in serial blood samples over a 24-hour period.
Precursor Preferences in Surfactant Synthesis of Newborns, 2005#	Study designed to better understand the potential differences in precursor preferences in surfactant synthesis between preterm infants with immature lungs and full-term infants with normal lung function. Protocol involved administration of labeled palmitate and acetate to both subject groups and, subsequently, measuring the incorporation of each infusion into surfactant collected by tracheal aspiration.
A Phase III Randomized Trial of Granulocyte Colony Stimulating Factor Stimulated Bone Marrow vs. Conventional Bone Marrow as a Stem Cell Source in Matched Sibling Donor Transplantation, 2008**	Protocol would compare granulocyte colony stimulating factor stimulated bone marrow with conventional bone marrow as a stem cell source in matched sibling donor transplantation. Study would be conducted in sibling pairs, one sibling acting as the bone marrow donor and the other receiving the bone marrow.

* Ross, (2005), op cit.

† Solicitation of Public Review and Comment on a Research Protocol: Sleep Mechanism in Children: Role of Metabolism, 68 Fed. Reg. 35415 (June 13, 2003).

‡ Solicitation of Public Review and Comment on Research Protocol: A MultiCenter Randomized Dose Response Study of the Safety, Clinical, and Immune Response of Dryvax® Administered to Children 2 to 5 Years of Age, 67 Fed. Reg. 66403, 66404 (Oct. 31, 2002); Irene Stiith-Coleman and David A. LePay, HHS, to Stewart Laidlaw. (2003, January 24). Determination Letter. Retrieved from <http://www.hhs.gov/ohrp/archive/dpanel/determ.pdf>.§ Solicitation of Public Review and Comment on Research Protocol: Effects of a Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder; a Functional Magnetic Resonance Study, 69 Fed. Reg. 47158, 47159 (Aug. 4, 2004); Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, HHS, FDA, Center for Drug Evaluation and Research. (2004, September 10). Transcript of Pediatric Ethics Subcommittee of the Pediatric Advisory Committee. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4066T1.htm>.¶ Office of Human Research Protections. (2007, February 23). Gonadotropin Releasing Hormone (GnRH) Agonist Test in Disorders of Puberty [Webpage]. Retrieved from <http://www.hhs.gov/ohrp/archive/children/gnrh.html>; Letter from Bernard

REASON REFERRED TO 407 REVIEW PANEL	PANEL DECISION
Research involved greater than minimal risk and offered no prospect of direct benefit to the individual children who were to be the healthy control participants.	Approved. The panel concluded that this protocol presented an opportunity to further the understanding of a serious condition affecting the health or welfare of children. Panelist concerns focused on radiation exposure during CT scans but the panel ultimately decided the protocol was approvable.
Research involved greater than minimal risk, offered no prospect of direct benefit, and proposed to enroll healthy children as participants.	Not approved. The panel concluded that there were not yet any data in adults.
Research involved greater than minimal risk, offered no prospect of direct benefit, and proposed to enroll healthy children as participants.	Not approved. The protocol was rejected because bioterrorism preparedness plans had evolved and the government no longer planned to use Dryvax for children.
Research involved greater than minimal risk and offered no prospect of direct benefit to the individual children who were to be the healthy control participants.	Approved. The panel concluded the protocol presented was a reasonable opportunity to further understanding of a serious condition affecting the health or welfare of children. Approval was conditioned on return of neuropsychological testing results to children and parents.
Research involved greater than minimal risk and offered no prospect of direct benefit to the individual children who were to be the healthy control participants.	Approved. The panel found that there was more than a minor increase over minimal risk for healthy children but that the study presented an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.
Research involved greater than minimal risk and offered no prospect of direct benefit to the individual children who were to be the healthy control participants.	Approved. The panel concluded that the study presented an opportunity to further understanding of a serious condition affecting the health or welfare of children.
Research involved more than a minor increase over minimal risk and offered no prospect of direct benefit to the healthy sibling donors.	Approved. The panel concluded that the study presented an opportunity to further understanding of a serious condition affecting the health or welfare of children.

A. Schwetz, Director, Office of Human Research Protections, Office of Public Health and Science, and Diane Murphy, Director, Office of Pediatric Therapeutics, FDA, to Mary Ellen Sheridan, Associate Vice President for Research, The University of Chicago. (2006, May 16). Retrieved from <http://www.hhs.gov/ohrp/archive/children/stipulat.pdf>; Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, HHS, FDA, Center for Drug Evaluation and Research. (2005, November 15). Transcript of Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, pp. 158-165. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4178t1.pdf>.

* Solicitation of Public Review and Comment on Research Protocol: Precursor Preference in Surfactant Synthesis in Newborns, 70 Fed. Reg. 30128 (May 25, 2005); Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, HHS, FDA, Center for Drug Evaluation and Research. (2005, June 28). Transcript of Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, pp. 202-222. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/05/transcripts/2005-4151t1.pdf>.

** Botkin, J.R., Professor, Pediatrics, University of Utah. (2008). Pediatric Ethics Subcommittee Meeting Summary: Presentation to Pediatric Ethics Subcommittee, December 9. [Slide Presentation]. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4406s1-01.pdf>; Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, HHS, FDA, Center for Drug Evaluation and Research. (2008, December 9). Transcript of Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, pp. 23-24. Retrieved from <http://www.fda.gov/ohrms/dockets/ac/08/transcripts/2008-4406t-01.pdf>.

Appendix III: Characteristics of Pathogens Classified by the National Institute of Allergy and Infectious Diseases, U.S. Department of Homeland Security, and U.S. Centers for Disease Control and Prevention as Posing the Greatest Risk to National Security and Public Health (Category A Biological Agents)*

Listed in the table below are the characteristics of various pathogens, determined by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, the U.S. Department of Homeland Security, and the U.S. Centers for Disease Control and Prevention to pose the greatest threat to U.S. security and public health. This class of pathogens is generally referred to as “Category A Biological Agents.” Pathogens designated as Category A Biological Agents are generally defined as follows: they (1) can be easily disseminated or transmitted between people, (2) cause high mortality rates with a potential for major impact on the public health, (3) carry the prospect of mass panic and social disruption, and (4) require special action for public health preparedness.†

* Adapted from: Email Correspondence from Richard Gorman, National Institute of Allergies and Infectious Diseases, NIH, to Kavita Berger, PCSBI. (2012, July 30).

† National Institute of Allergy and Infectious Disease (NIAID). (2012, February 27). Category A, B, and C Priority Pathogens, National Institutes of Health [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/biodefenselated/biodefense/pages/cata.aspx#>.

CATEGORY A BIOLOGICAL AGENTS

Name	Organism type	Transmission	Estimated Mortality: Untreated	Estimated Mortality: Treated
Anthrax* (inhalational) <i>Bacillus anthracis</i>	Bacteria	Inhalation of aerosolized spores	90%	75%
Botulism† <i>Clostridium botulinum</i>	Bacteria	Spore toxin transmitted through food sources	25%	6%
Plague‡ <i>Yersinia pestis</i>				
Bubonic Plague	Bacteria	Bite from infected flea or rodent	50-60%	5-14%
Pneumonic Plague	Bacteria	Inhalation of plague bacteria Secondary infection due to untreated bubonic or septicemic plague	~100%	36-57%
Septicemic Plague	Bacteria	Bite from infected flea or rodent Secondary infection due to untreated bubonic or pneumonic plague	~100%	22-28%

* For additional anthrax references, see: Inglesby, T.V., et al. (1999). Anthrax as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 281(18), 1735-1745; CDC. (2012). Questions and answers about anthrax [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/anthrax/faq/>; CDC. (2006). Anthrax: What you need to know [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/anthrax/needtoknow.asp>; NIAID. (2010). Anthrax [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/anthrax/Pages/default.aspx>.

† For additional botulinum toxin references, see: Arnon, S.S., et al. (2001). Botulinum toxin as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 285(8), 1059-1070; CDC. (2001). Facts about botulism [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/botulism/factsheet.asp>; NIAID. (2010). Botulism [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/botulism/Pages/default.aspx>.

	Medical Countermeasures	Cause of Death	Unique Pediatric Vulnerability	Why a Potential Threat
	Vaccines and antibiotics are available Antitoxins are in development	Pneumonia	Close to ground Higher respiratory rate	Bacteria is found worldwide Capability exists to produce and aerosolize large amounts of spores
	Antitoxins are available	Suffocation, muscle paralysis	Smaller size Hand to mouth behavior	Extreme lethality and potency (a single gram could kill 1 million people) Ease of production, transportation, and misuse Need for prolonged intensive care for infected patients
	Antibiotics are available	Pneumonia, shock, sepsis	Higher respiratory rate Curiosity Less fluid reserve	sBacteria exist in many labs Long history of use as biological weapon Person-to-person spread

† For additional plague references, see: Inglesby, T.V., et al. (2000). Plague as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 283(17), 2281-2290; CDC. (1997). Fatal human plague: Arizona and Colorado 1996. *Morbidity and Mortality Weekly Report*, 46(27), 617-620; CDC. (2012). Plague: Frequently asked questions [Webpage]. Retrieved from <http://www.cdc.gov/plague/faq/>; CDC. (2012). Plague: Maps and statistics [Webpage]. Retrieved from <http://www.cdc.gov/plague/maps/index.html>; CDC. (2005). Frequently asked questions about plague [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/plague/faq.asp>; CDC. (2001). Facts about plague [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/plague/factsheet.asp>; NIAID. (2007). Plague [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/plague/Pages/default.aspx>.

CATEGORY A BIOLOGICAL AGENTS

Name	Organism type	Transmission	Estimated Mortality: Untreated	Estimated Mortality: Treated
Small Pox* <i>Variola major</i>	Virus	Inhalation of infected respiratory drops Contact with infected individual	30%	No treatment available
Tularemia† <i>Francisella tularensis</i>	Bacteria	Bites from fleas, ticks, or infected animals	5-60%‡	2%
Viral Hemorrhagic Fevers§				
Arenavirus (Lassa Fever)	Virus	Inhalation or ingestion of virus via rat fecal particles Contact with infected fluids	75-78%	15-20%
Filovirus (Ebola & Marburg)	Virus	Contact with infected bodily fluids	Ebola: 50-90% Marburg: 23-90%	No treatment available

* For additional smallpox references, see: Henderson, D.A., et al. (1999). Smallpox as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 281(22), 2127-2137; CDC. (2009). Questions and answers about smallpox disease [Webpage]. Retrieved from http://www.bt.cdc.gov/agent/smallpox/faq/smallpox_disease.asp; CDC. (2004). Smallpox disease overview [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/smallpox/overview/disease-facts.asp>; NIAID. (2008). Smallpox [Webpage] Retrieved from <http://www.niaid.nih.gov/topics/smallpox/Pages/default.aspx>.

† For additional tularemia references, see: Dennis, D.T., et al. (2001). Tularemia as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 285(21), 2763-2773; CDC. (2011). Tularemia [Webpage]. Retrieved from <http://www.cdc.gov/tularemia/>; CDC. (2003). Key facts about tularemia [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/tularemia/facts.asp>; CDC. (2003). Frequently asked questions about tularemia [Webpage]. Retrieved from <http://www.bt.cdc.gov/agent/tularemia/faq.asp>; NIAID. (2012). Tularemia [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/tularemia/Pages/default.aspx>.

‡ Variations depend on the strain and severity of infection.

§ A few examples of viral hemorrhagic fevers are provided in the table above. This list is not exhaustive. For additional hemorrhagic fever references, see: Borio, L., et al. (2002). Hemorrhagic fever viruses as a biological weapon: Medical and public health management. *Journal of the American Medical Association*, 287(18), 2391-2405; McCormick, J.B., et al. (1986) Lassa fever: Effective therapy with Ribavirin. *The New England Journal of Medicine*, 314(1), 20-26; CDC. (2012). Questions and answers about Marburg hemorrhagic fever [Webpage]. Retrieved from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/marburg/qa.htm>; CDC. (2012). Lassa fever [Webpage]. Retrieved from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/lassaf.htm>; CDC. (2012). Questions and answers about Ebola hemorrhagic fever [Webpage]. Retrieved from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/ebola/qa.htm>; CDC. (2012). Arenaviruses [Webpage]. Retrieved from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/arena.htm>; CDC. (2011). Viral hemorrhagic fevers [Webpage]. Retrieved from <http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/vhf.htm>; NIAID. (2013). Ebola/Marburg [Webpage]. Retrieved from <http://www.niaid.nih.gov/topics/ebolaMarburg/Pages/default.aspx>.

	Medical Countermeasures	Cause of Death	Unique Pediatric Vulnerability	Why a Potential Threat
	Vaccine is available Antivirals are in development	Pneumonia, secondary skin infections	Higher respiratory rate Hand to mouth behavior	Virus exists in few labs Person-to-person spread Specific therapy is lacking
	Antibiotics are available	Pneumonia	Curiosity	Infects over 100 animal species Ability to be aerosolized As few as 10 bacteria can cause infection Can survive at low temperatures
	Ribavirin therapy Only supportive treatments	Hemorrhagic diathesis, shock, multi-organ system failure	Curiosity Close to ground	Could have a high case fatality rate Some are endemic in central Asia and southern Africa Can be aerosolized

Appendix IV: An Ethical Framework to Guide National-Level Review of Pediatric Medical Countermeasure Research under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54

The following ethical framework is intended to guide the review of any pre-event pediatric medical countermeasure research protocol that cannot be designed to pose only minimal risk and therefore rises to the level of national-level review under 45 C.F.R. § 46.407 and/or 21 C.F.R. § 50.54. Importantly, any such protocol should pose no more than a minor increase over minimal risk.

1. Does the research present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem that could affect the health or welfare of children?

- A. Serious problem, as judged by:
 - i. Consequences of exposure
 - ii. Likelihood (or threat) of exposure
 - iii. “Vital importance”
- B. Reasonable opportunity

2. Will the research be conducted in accordance with sound ethical principles?

- A. Ethical threshold of acceptable risk and adequate protection from harm
- B. Ethical research design
 - i. Scientific necessity
 - ii. Research plan
 - a. Scientific validity
 - b. Small trials and age de-escalation
 - c. Appropriate monitoring
 - d. Proper planning for post-event research
 - iii. Prior adult testing to minimize risk to children
 - iv. Sufficient benefit over alternatives
 - v. Fair subject selection
- C. Post-trial requirements to ensure ethical treatment of children and their families
 - i. Distribution protocol for all children tested or assured
 - ii. Compensation for research-related injury
- D. Community engagement in pre-event research
- E. Transparency and accountability

3. Are adequate provisions made for soliciting the permission of parents or guardians and the meaningful assent of children?

Appendix V: Example of Differences between Active and Passive Surveillance Studies

This chart demonstrates visually the stark differences between active and passive surveillance studies. During active surveillance, the patient is actively followed and asked pointed and specific questions about the reactions they might be experiencing. The healthcare provider or researcher can evaluate directly the severity of those reactions because there is direct communication. Passive surveillance, however, involves individuals self-reporting and can occur at any time post-administration. As a result, the data are less precise and are self-selected based on those patients who are more apt to report an adverse event. In addition, the data might be less specific and follow-up data on the patient’s overall health status might not be as readily available as they are in active surveillance.

TIME FROM VACCINE ADMINISTRATION	ACTIVE SURVEILLANCE	PASSIVE SURVEILLANCE
0	Vaccine administration	Vaccine administration
30 minutes	Participant completes reaction questionnaire	Participant leaves health care facility
1 day	Repeat questionnaire	At any time, participant may call in to the Vaccine Adverse Event Reporting System and report a possible adverse event; the patient may be contacted for follow-up, such as release of medical records for data analysis
2 days	Repeat questionnaire	
3 days	Repeat questionnaire	
4 days	Repeat questionnaire	
5 days	Repeat questionnaire	
1 week	Repeat questionnaire Participant’s blood is drawn for immunogenicity study	
2 weeks	Repeat blood draw	
4 weeks	Repeat blood draw	

Adapted from: IOM. (2002). *The Anthrax Vaccine: Is it Safe? Does it Work?* Washington, DC: National Academies Press.

Appendix VI: Glossary of Key Terms Related to Pediatric Medical Countermeasure Research

Adverse event: An undesired medical occurrence that presents itself during treatment with a medical product, which may or may not have been caused by the treatment.

Adverse reaction: An undesired side effect of a medical treatment or drug.

Age de-escalation: Conducting trials first in adults, then with older children, and then with progressively younger children as appropriate in order to prevent undue risk to young children.

Agent (chemical or biological): A biological substance or chemical compound that can be used purposefully as a weapon to cause sickness or death.

Anthrax: An infectious disease caused by *B. anthracis* spores, which can be contracted in humans either by inhalation, skin contact, or ingestion.

Antibiotics: Medicines that are used for the treatment or prevention of bacterial infections.

Antibody: Protein that is used by the immune system to recognize and fight bacteria, viruses, and other substrates that appear foreign or harmful.

Anthrax vaccine adsorbed (AVA): An FDA-licensed human anthrax vaccine approved for use in those 18–65 years of age who are at high risk of exposure.

Biohazard: A biological agent that is a hazard to humans or the environment.

Clinical trial: A research study designed to answer a specific question regarding the effectiveness and safety of drugs, biologics, or medical devices.

Common Rule: Federal regulations that govern human subjects research; also known as the Federal Policy for the Protection of Human Subjects, adopted by 18 federal departments and agencies.

Cutaneous anthrax: An infection caused by *B. anthracis* that is limited to the skin.

Dark Zephyr: An exercise conducted by the U.S. government in early 2011 to test local, state, and federal government responses to a large-scale anthrax release in a major metropolitan area.

Dosage: The prescribed frequency, quantity, and size of doses of a therapeutic agent to be administered to a patient.

Dose: The amount of a medication to be administered.

Efficacy: The ability of a medical product or treatment to produce the desired therapeutic effect.

Emergency use authorization (EUA): An authorization issued by FDA to allow either the use of an unapproved medical product or an unapproved use of an approved medical product during a declared emergency.

Immune response: The process through which the body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful.

Immunization: The process by which a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.

Immunogenicity: The ability or degree to which a substance can produce an immune response.

Inhalational anthrax: An infectious disease caused by breathing in the spores of the bacteria *B. anthracis*.

Investigational new drug application (IND): An application submitted to FDA before studying a drug or biologic in humans.

Medical countermeasure (MCM): FDA-regulated products and interventions used in response to chemical, biological, radiological, and nuclear attacks.

Metabolic: Having to do with the chemical reactions involved in the body's use of energy.

Off-label use: The practice of prescribing a medical product for use not in accordance with that approved by FDA.

Pathogen: A microorganism that causes disease; for example, *B. anthracis* is the pathogen that causes anthrax.

Pharmaceutical: A medicinal drug.

Prophylaxis: Measures taken to prevent disease before the onset of signs or symptoms of infection.

Reactogenicity: The ability of a vaccine to cause expected negative or adverse reactions.

Research protocol: A plan detailing the methods of a research study as well as the detailed plan for collecting and analyzing data, and ensuring quality and safety.

Spores: Small, usually one-celled organisms that can give rise to other organisms without interacting with one another under favorable conditions.

Strategic National Stockpile (SNS): The United States' national repository of antibiotics, chemical antidotes, vaccines, antitoxins, life-support medications, intravenous administration and airway maintenance supplies, and medical/surgical items to be used in the case of a public health emergency.

Subpart D: A stringent set of additional research protections for children that supplement those protections provided for federally supported or regulated human subjects research more broadly.

Systemic: Relating to or affecting multiple organ systems or the entire human body.

Vaccine: A product that improves immunity to a particular disease.

Vaccine Adverse Event Reporting System (VAERS): The United States' national vaccine safety surveillance program that collects information about adverse events that occur after the administration of vaccines. Data submitted to VAERS are analyzed and made available to the public.

Vector: An organism that carries disease-causing microorganisms from one host to another.

Appendix VII: Guest Presenters to the Bioethics Commission Regarding Pediatric Medical Countermeasure Research

Michael R. Anderson, M.D., F.A.A.P.

Vice President and Chief Medical Officer,
UH Case Medical Center; Associate
Professor of Pediatric Critical Care,
Case Western Reserve University; Chief
Medical Officer, UH Rainbow Babies and
Children's Hospital; Member and Fellow,
American Academy of Pediatrics

Tom L. Beauchamp, Ph.D.

Professor of Philosophy,
Senior Research Scholar,
Kennedy Institute of Ethics,
Georgetown University

Georges Benjamin, M.D.

Executive Director,
American Public Health Association

Ruth Berkelman, M.D.

Rollins Professor and Director,
Center for Public Health Preparedness
and Research, Emory University

David DeGrazia, Ph.D.

Professor of Philosophy,
George Washington University

Alan R. Fleischman, M.D.

Clinical Professor, Department of
Pediatrics, Department of Epidemiology
and Population Health, Albert Einstein
College of Medicine, Yeshiva University

Richard Gorman, M.D.

Head, Pediatric and Obstetrics Integrated
Program Team, HHS Office of the
Assistant Secretary for Preparedness and
Response; Associate Director for Clinical
Research, Division of Microbiology and
Infectious Disease, National Institute of
Allergy and Infectious Diseases, National
Institutes of Health

Neal Halsey, M.D.

Professor of International Health,
Johns Hopkins Bloomberg School of
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